Oscillatory Positive Expiratory Pressure (OPEP) Therapy in COPD

A thesis submitted for the degree of Doctor of Philosophy (PhD)

May 2022

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Declaration of Novelty

In this thesis, I declare that I wrote it entirely myself and that it is my own original work unless otherwise stated. I referenced sources and other works as appropriate. This is the first time this work has been submitted for assessment in a higher degree application.

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Acknowledgement

All praise for Allah (The All Mighty) and His blessings for successful completion of my thesis.

At this achievement moment, first and foremost, I would like to express my gratitude to my PhD supervisors Professor Nick Hopkinson, Professor Mike Polkey, and Professor Surinder Birring. I am very grateful for your support and valuable input to complete this thesis. This thesis would not have been possible without the guidance, support, patience of Professor Hopkinson. Professor Polkey has been an inspiration throughout the process of creating this thesis, and I am extremely grateful for his boundless passion and support. I am grateful for Professor Birring for providing support and assistance in training and advising regarding cough monitoring and cough analysis described in this thesis.

I also would like to thank Dr James Allinson for being a mentor during my PhD.

I also wish to thank the muscle lab team, especially Dr Ali Alasmari and Dr Abdullah Alsulayyim, and Dr Ruth Barker, for being always willing to help, Dr Keir Philip for training me in sleep actigraphy, Dr Adam Lewis for introducing me to the pulmonary function test team, and Dr Winston Banya for the statistical advice. Thank you also to the O-COPD trial participants - without their work, my thesis would not be possible.

Finally, I am thankful for my whole family for their patience, love, and support throughout my journey. For beautiful my parents, Mardy and Hudia, who inspired me and supported me to achieve my higher education goal. For my beloved wife, Noha with whom we have our gorgeous daughter (Noor) at the 1st year of my PhD. For my siblings who always provided me with boundless encouragement.

Dedications

To my parents and my wife (Noha), as well as my daughter (Noor), who have provided me with unwavering support, understanding, love, and encouragement throughout my PhD journey, I dedicated this thesis.

Publications arising from this thesis

- S.M. Alghamdi, R. E. Barker, A. S. Alsulayyim, A. M. Alasmari, W. A. Banya, M. I. Polkey, S. S. Birring and N. S. Hopkinson (2020). "Use of oscillatory positive expiratory pressure (OPEP) devices to augment sputum clearance in COPD: a systematic review and meta-analysis." **Thorax** 75(10): 855-863.

Paper drafted and submitted for publication

- Alghamdi SM et al. Oscillatory Positive Expiratory Pressure (OPEP) Therapy in Chronic Obstructive Pulmonary Disease (COPD): The O-COPD Trial. Accepted in Thorax.

Conference oral presentations

- Alghamdi SM et al. Oscillatory Positive Expiratory Pressure (OPEP) Therapy in Chronic Obstructive Pulmonary Disease (COPD): The O-COPD Trial (ATS assembly, May 13, 2022).

Poster presentations – published

- Alghamdi SM et al. Cough Frequency in Chronic Obstructive Pulmonary Disease (COPD) with Frequent Sputum Production (ATS assembly, May 13, 2022).
- Alghamdi SM et al. Impact of Oscillatory Positive Expiratory Pressure (OPEP) Therapy on Objectively Determined Cough and Sleep Disturbance in COPD: A Sub-Study from the O-COPD Trial (ATS assembly, May 13, 2022).

COVID-19 impact statement

A portion of this thesis was interrupted by the COVID-19 pandemic. The interruption includes suspension to research activity, lack of access to research facilities, lack of access to potential participants, and libraries. Other issues related to the COVID-19 interruption are discussed in the relevant chapters.

Thesis Summary

People with chronic obstructive pulmonary disease (COPD) commonly have a productive cough due to mucus hypersecretion. Clearing mucus from the chest can be difficult, as lung hyperinflation, respiratory muscle dysfunction and premature airway collapse impede the ability to generate an effective cough. Airway Clearance Techniques (ACTs) with the use of oscillating positive expiratory pressure (OPEP) devices can be added to the usual care for sputum clearance. However, assessment of the effect of OPEP devices is so far based on short-term studies with low-grade evidence and there is a lack of information regarding their long-term impact and effectiveness. In this thesis, I have four results chapters to discuss this gap. First, using accepted systematic review methodology to rigorously examine the current evidence on the use of OPEP devices for the treatment of cough and sputum clearance in patients with COPD who frequently produce sputum. Second, conduct a randomised clinical trial (acronym: O-COPD) to evaluate the impact of an OPEP device (the Acapella) on the health-related quality of life in patients with COPD over three-months. Third, study cough characteristics and its relationship to overnight sleep disturbances. Fourth, evaluate the impact of an OPEP device (the Acapella) on cough frequency and sleep actigraphy in a subset of the O-COPD group. In summary, results from the O-COPD trial, coupled with the systematic review, can address the concerns raised regarding the long-term effectiveness of OPEP devices in treating sputum aspects in stable COPD patients. COPD patients with sputum production who received OPEP treatment for three months, compared to the usual care, demonstrated better disease management and improvement in general and cough-related quality of life (LCQ). The findings suggest that adding the OPEP device is effective in optimising the usual care and, perhaps, can be the new mode of usual care in managing cough and sputum

production in COPD patients. Larger and longer clinical trials are required to guide the long-term use of OPEP and patient selection.

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1 Introduction and literature review

1.1 Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a common, progressive respiratory disease characterised by persistent airflow limitation and respiratory symptoms due to airway and alveolar abnormalities (GOLD 2020). It can affect the alveolar sacs or bronchioles and then cause emphysema or chronic bronchitis (CB), respectively. Patients with COPD can have abnormalities in the airways or alveoli or a mixture of both. These abnormalities are mostly induced by chronic inflammatory responses due to continuous exposure to noxious substances, classically tobacco smoke (Main, Grillo et al. 2015, GOLD 2020). The disease usually affects middle-aged and elderly people (>40 years old) and is often associated with other comorbidities. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) is a worldwide association that provides guidelines for the diagnosis, treatment, prevention, and management of COPD, assesses the characteristics of COPD globally, and maximises available resources to support COPD care (GOLD 2017, GOLD 2020, GOLD 2021).

1.2 Prevalence

COPD is an increasingly common cause of morbidity and mortality and will be the third leading cause of death by 2030 (Mathers and Loncar 2006). This increase in COPD prevalence is mostly due to an increase in smoking and the impact of ageing on the lungs (Fletcher and Peto 1977). Smokers are at greater risk of developing COPD than non-smokers and it is mostly prevalent more among men than women (Fletcher and Peto 1977, Løkke, Lange et al. 2006, Buist, McBurnie et al. 2007). In addition to the classical risk factors for COPD, other factors can contribute to the

development of COPD, such as childhood asthma, inhalation of dust, passive smoking, biomass fuels, and outdoor air pollution (Buist 1996, Main and Denehy 2016). Genetically inherited disorders, such as alpha-1 Antitrypsin deficiency, have also been found to be associated with the development of COPD, with or without smoking history. In view of all of these facts, it is important to mention that COPD is not just one respiratory disease but a group of respiratory and non-respiratory diseases, and it can be difficult to differentiate COPD from other underlying chronic respiratory diseases, such as asthma (Tinkelman, Price et al. 2006, Spiro, Silvestri et al. 2012).

1.3 Aetiology

Cigarette smoking is the most common aetiological factor for COPD although biomass fuels are recognised to be important in some parts of the world (Løkke, Lange et al. 2006, Hopkinson, Hart et al. 2017, van Dorn 2017). A causal relationship has also been identified between occupational dust exposure and mucus secretion, which eventually leads to airflow obstruction (Albert, Spiro et al. 2008). Airflow obstruction is generally caused by inflammation resulting from innate immune responses to inhaled products of burned tobacco or other noxious gases (Figure 1.1). Such inflammatory responses target the epithelial lining and the mucus glands, which increases mucus production, reduces mucociliary function, and increases the permeability of the airspace epithelial barriers (Nadel, Murray et al. 2000). Also, there is an epidemiological evidence that children with asthma most likely at risk of developing COPD in the future (Tai, Tran et al. 2014).

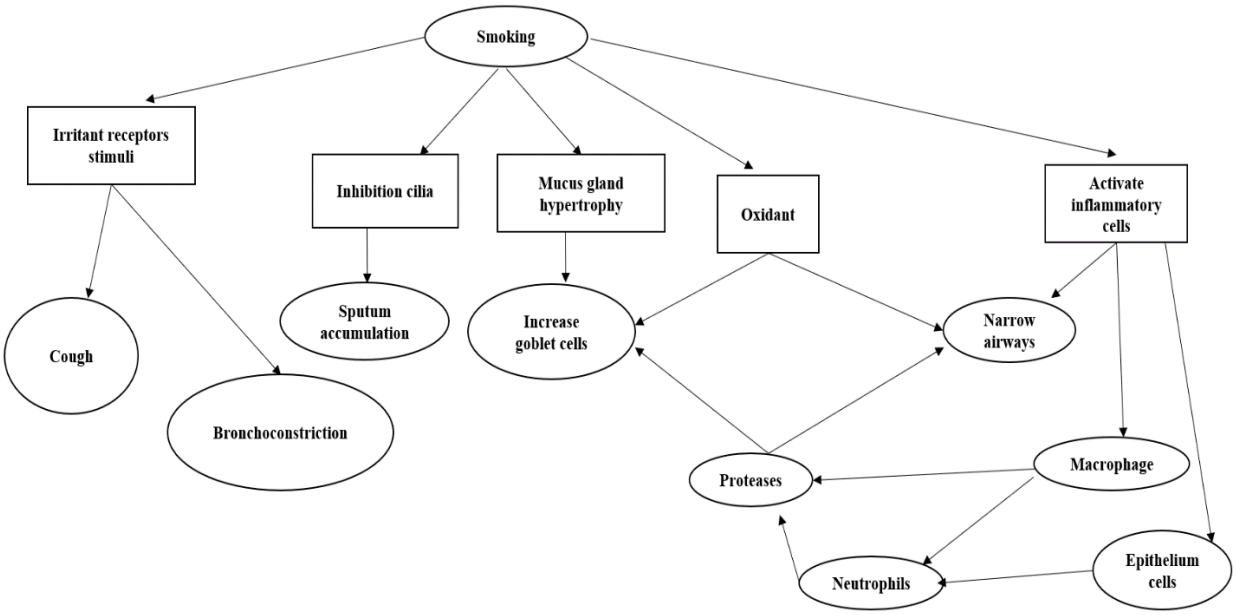


Figure 1.1 Cigarette smoking and sputum production

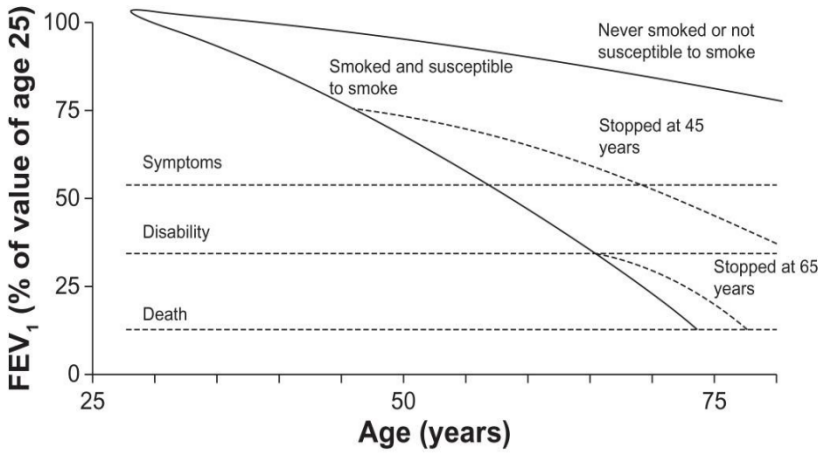
1.4 COPD pathophysiology

Despite the advances in our understanding of the pathology of COPD in recent years, the pathological features of COPD are complex and there is still much to be discovered (MacNee 2005, Spiro, Silvestri et al. 2012). So far, we know that exposure to tobacco smoke and noxious particles trigger an inflammatory response in the lungs (Barnes, Shapiro et al. 2003, Chung and Adcock 2008, Agustí and Vestbo 2011). The inflammatory response can vary, but there is some certainty that all smokers have inflammation in their lungs (Agusti, Calverley et al. 2010, Agustí and Vestbo 2011). In smokers who develop COPD, it seems that the inflammation process is enhanced and fails to be resolved (Gonçalves, Coletta et al. 2011). Figure 1.2

There was classically a relationship between smoking history and a decline in the spirometer parameters, particularly the forced expiratory volume in one second (FEV1) predicted (Fletcher, Peto et al. 1976, Fletcher and Peto 1977). However, the same smoking background for different

people is not necessarily accompanied by the same clinical presentations and respiratory symptoms. This variation is due to the different underlying pathological changes that range from airway obstruction and chronic bronchitis to widespread emphysema and hyperinflation, or it can be mixed to a varying extent. Thus, the mechanisms of these underlying pathological changes, as well as the disease progression, are complex (Mason, Broaddus et al. 2010).

Figure 1.2 Modified graph of Fletcher and Peto that demonstrate the decline in lung function and its association with smoking, aging, COPD symptoms, disability, and death.



1.4.1 Pathological features of COPD

Pathological changes in COPD lead to lung hyperinflation, insufficient gas exchange, dyspnoea, reduced exercise tolerance, skeletal muscle dysfunction, and reduced cardiac output.

1.4.2 Airflow limitations and lung hyperinflation

Premature closure of the airways and destruction of the lung parenchyma lead to a reduction in the expiratory time. This reduction in the expiratory time causes expiratory flow limitation, which results in air trapping and hyperinflation. This is known as static hyperinflation. Mechanically, this hyperinflation flattens the diaphragm and makes it short, which contributes to difficulty in

breathing and airflow limitation. This airflow limitation becomes greater during physical exertion, hyperinflation increases and the breathing pattern is impacted, causing exertional dyspnoea (O'donnell 2001).

1.4.3 Insufficient gas exchange

Destruction of the alveoli and capillaries in COPD leads to a ventilation/prefusion (V/Q) mismatch. As this V/Q mismatch increases, patient oxygen desaturation and demand for breathing increase, causing dyspnoea and cyanosis in some cases (O'donnell and Laveneziana 2006, Main and Denehy 2016). Impaired gas exchange is mostly caused by emphysema, and it can be more intense during sleep and exercise (Kent, Mitchell et al. 2011).

1.4.4 Dyspnoea

Dyspnoea is the key symptom in COPD. Pathological changes due to hyperinflation and abnormal gas exchange can cause dyspnoea in COPD. Dyspnoea can vary from one patient to another based on the level of exercise and the degree of airway obstruction. In COPD, the experience of breathlessness and dyspnoea can also increase overnight or during sleep (Lange, Marott et al. 2014). Patients with mild COPD experience less dyspnoea during everyday activities than those with moderate to severe COPD.

1.4.5 Reduced exercise tolerance

Exercise with COPD can be limited by ventilatory, cardiac or skeletal muscle constraints. Pathophysiological changes in the lungs, such as airflow limitation, hyperinflation, and abnormal gas exchange, are major constraints to the ventilatory process and ultimately reduce the tolerance to exercise (Watz, Waschki et al. 2009). With COPD, this limitation is mostly caused by

exertional dyspnoea; however, hyperinflation that impede cardiac output as well as chronic heart disease or skeletal muscle dysfunction can contribute in reducing exercise tolerance (O'donnell 2001, Main and Denehy 2016).

1.5 Diagnosis

When diagnosing individuals with COPD, the history of respiratory symptoms, such as cough, sputum production, breathlessness, wheezing, as well as cigarette smoking and/or exposure to noxious gases or occupations dust, must be considered (Spiro, Silvestri et al. 2012). A correct diagnosis of COPD is crucial to provide prompt management for patients with COPD. In general, the diagnosis of COPD depends on a patient's history, physical examinations, and pulmonary function test (PFT) results (GOLD 2017). However, the literature indicates that there is a high rate of diagnostic error, primarily because general practitioners either under- or over-diagnose COPD (Tinkelman, Price et al. 2006, José, Camargos et al. 2014). COPD is one of the most prevalent causes of early mortality and excessive economic burden on healthcare systems (Raherison and Girodet 2009). In 2015, 3.2 million people died worldwide because of COPD (Soriano, Abajobir et al. 2017). The British Lung Foundation reports that there is increasing prevalence of COPD in the United Kingdom (UK), with more than 1.2 million people currently diagnosed with the disease. Assumptions on the prevalence of COPD in many countries around the world may be underestimated because a significant number of people with COPD remain clinically undiagnosed (Tinkelman, Price et al. 2006). Recently, advance approaches such as artificial intelligence and machine learning have been proposed to promote timely and accurate COPD diagnosis (Das, Topalovic et al. 2018, Mekov, Miravitlles et al. 2020, Kaplan, Cao et al. 2021).

1.5.1 Pulmonary function testing

Spirometry is an objective test generally used to confirm airflow limitation in COPD. Spirometry parameters have specific diagnostic criteria for COPD. Force expiratory volume in one second (FEV1) / force vital capacity (FEV1/FVC) ratio is usually used to confirm COPD. To obtain a COPD diagnosis, a patient must have irreversible airflow limitation and a ratio of FEV1/FVC of less than 0.70; otherwise, there may be a different respiratory condition (Spiro, Silvestri et al. 2012). Patients with COPD are classified into different categories based on the severity of airflow limitations and respiratory symptoms. The GOLD guidelines classify airflow limitation into four main categories: ABCD. “I category represent “mild”, “II” category represents “moderate”, “III” category represents “severe”, and “IV” category represents “very severe”, based on the degree of airway obstruction in patients with COPD (GOLD 2017). COPD is a heterogenous disease and it has different clinical phenotypes (Han, Agusti et al. 2010). This clinical phenotyping helps to classify individuals with COPD into subgroups based on the distinct clinical presentations, pathological features, and the rate of illness progression or response to therapy (Table 1.1). Current phenotypes include chronic bronchitis , emphysema, or a mixture of both (Han, Agusti et al. 2010).

Table 1.1 COPD classification based on FEV1/FVC ratio < 0.70 also known as GOLD.

Lung volume parameter	**Airflow limitation categories**		
FEV1≥ 80% predicted	I	Mild	GOLD 1
80% ≤ FEV1 < 80% predicted	II	Moderate	GOLD 2
30% ≤ FEV1 < 50% predicted	III	Severe	GOLD 3

FEV1 < 30% predicted	IV	Very Severe	GOLD 4

1.5.2 Emphysema

Emphysema is defined histologically as an enlargement of the distal airspace to the terminal bronchioles. This enlargement is due to the destruction of the lung tissue, mostly the alveolar walls, and attachment to the outer adjunct of the alveolar wall (Fletcher 1978, Fletcher and Pride 1984, Nadel, Murray et al. 2000, Celli, MacNee et al. 2004, Spiro, Silvestri et al. 2012). Emphysema mostly describes the damage in the lung parenchyma and acinar unit. This may be clustered around the terminal bronchioles, which is known as centrilobular emphysema (Kim, Eidelman et al. 1991). Centrilobular emphysema mostly appears in the upper lobe and is associated with a smoking history (Kim, Eidelman et al. 1991). The other pattern is called panlobular emphysema, which occurs when there is damage throughout the whole acinar unit (Kim, Eidelman et al. 1991). With these anatomical changes and the inflammatory profile in the airways, the lungs lose the support structure of the alveolar wall and the outer attachments. This leads to reduced lung recoil, premature collapse of the airways, air trapping, and airflow limitation (Nadel, Murray et al. 2000, Spiro, Silvestri et al. 2012).

1.5.3 Chronic bronchitis

Chronic bronchitis (CB) in clinical terms refers to the presence of a cough and sputum production on most days for at least three months in the last two consecutive years (Fletcher 1978, Fletcher and Pride 1984, Nadel, Murray et al. 2000, Celli, MacNee et al. 2004). It represents inflammation in the airways, predominantly in the mucus glands and inflammatory cells. Due to continual exposure to smoke in the large airways, infiltration of the inflammatory cells increases, mostly

by macrophages and $CD8^+$ T lymphocytes (O'Shaughnessy, Ansari et al. 1997). This infiltration is compounded by an increase in the number and distribution of the goblet cells in the bronchial wall epithelium surface. This chronic inflammation causes mucus hypersecretion, impairs mucociliary clearance, and increases the permeability of the airspace epithelium barriers, resulting in airway obstruction (Hogg, Chu et al. 2004).

Evidence shows that COPD patients with chronic bronchitis have worse lung function, more respiratory symptoms and exacerbation events, limited physical activity, and a higher mortality rate (Lange, Nyboe et al. 1990, Seemungal, Donaldson et al. 1998, Pelkonen, Notkola et al. 2006, Burgel, Nesme-Meyer et al. 2009, de Oca, Halbert et al. 2012, Corhay, Vincken et al. 2013). The data from the Lung Health Study showed that aggressive smoking cessation intervention can significantly contribute to slower the decline in lung functions and respiratory symptoms(Anthonisen, Connett et al. 1994, Anthonisen, Connett et al. 2002). There is growing research to evaluate to what extent the presence of a cough and sputum production in chronic bronchitis influences sleep quality and nighttime rest in COPD populations (Hartman, Prinzen et al. 2015, Fischer, Gross et al. 2018, Spina, Casale et al. 2021).

1.6 Cough and sputum production as clinical features

Cough, sputum production, and dyspnoea are prominent symptoms among many COPD patients (Kinsman, Yaroush et al. 1983, Rennard, Decramer et al. 2002). Excessive sputum in the airways is a traditional characteristic of chronic bronchitis. Together with other pulmonary and extrapulmonary conditions, chronic bronchitis is part of the COPD family (Rogers 2007). In COPD, coughing and sputum production are attributed to different reasons, including inflamed airways, smoking, comorbidities, acute exacerbations, and other unknown factors. Many COPD patients

experience coughing and sputum production during a specific time in the year, which could vary from one subject to another. Clinical studies also show that persistent sputum producers have worse clinical characteristics, as well as an increase in inflammatory mediators in the airways (Khurana, Ravi et al. 2014). Evidence also shows that coughing and sputum production are associated with recurrent exacerbations and hospital admissions, as well as gastroesophageal reflux disease (GERD) (Burgel, Nesme-Meyer et al. 2009, Miravitlles 2011, Benson, Müllerová et al. 2015). Persistent sputum production, therefore, exists in a subgroup of COPD, where the patients experience excessive sputum production every day of the year. Persistence sputum production can be accompanied by or without chronic cough, depending on the severity of the symptoms (Allinson, Hardy et al. 2016). Clinical research has recently found a useful way of classifying patients into sputum producers and non-sputum producers based on the amount of sputum being expectorated daily. This classification is used in data analysis to obtain a conclusion about the effect of treatments on that subgroup (Hartman, Prinzen et al. 2015, Svenningsen, Paulin et al. 2016).

1.6.1 Cough definitions

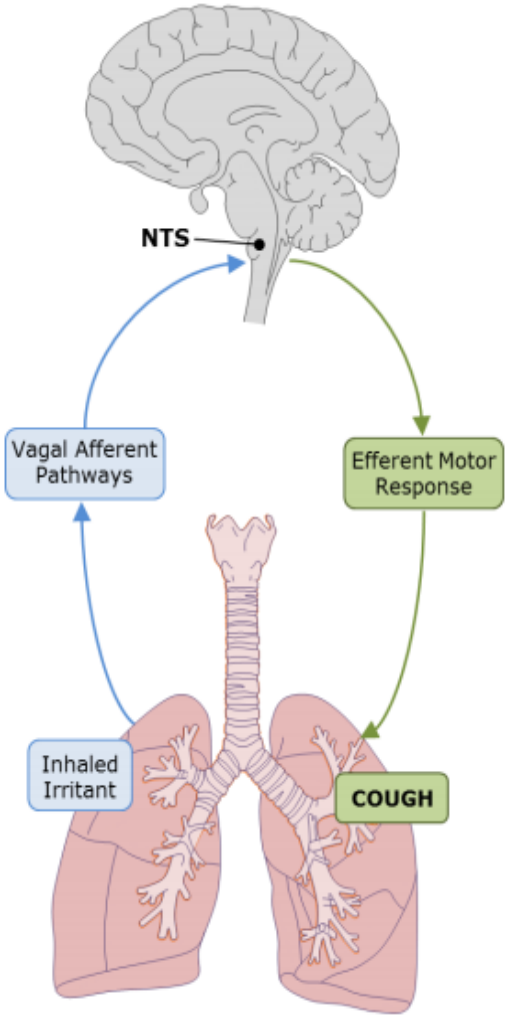
Cough as a respiratory symptom is defined as a normal defence mechanism that protects the respiratory system from noxious substances, toxic material, viral and/or bacterial infections, and helps in clearing secretions from the airways (Nadel, Murray et al. 2000, Spiro, Silvestri et al. 2012). A cough can be productive or non-productive. A productive cough or wet cough describes when the cough itself is able to remove mucus or secretions from the lungs while a non-productive or dry cough is the opposite (Chung and Pavord 2008, Cho, Birring et al. 2019). A

cough can be induced voluntarily (Nemati, Rahman et al. 2020), but an involuntary cough is initiated from the vagus nerve and its branches (Chung and Pavord 2008).

1.6.2 Mechanism of cough

Coughing is the outcome of a complex relationship between lung structures and the human brain (Figure 1.3). At the lung level, the mechanism of the cough is provoked when afferent nerve receptors are stimulated by inhalation of noxious substances such as cigarette smoke. The nasal cavity, larynx, pharynx, carina, and trachea are the most sensitive areas that trigger a cough, all of which are innervated by the vagus nerve (Widdicombe 1995). Cough receptors are also known as “irritants” and can be found outside the lung structure, such as in the oesophagus, diaphragm, and stomach, which explains why coughs can also be generated by aspirated food or foreign bodies (Widdicombe 1995). When these cough receptors are activated by chemical and mechanical stimuli, the afferent nerve modulates the cough response. At the brain level, feedback from the medulla can initiate a rapid change in the lung mechanics, such as the depth and frequency of breathing, inducing cough reflux (Chung, Widdicombe et al. 2003).

Figure 1.3 The mechanism and the simple neurophysiology of the cough reflex. NTS: Nucleus Tractus Solitarius at the brainstem (Holt 2015).



1.6.3 Cough phases

The cough reflex consists of a series of respiratory manoeuvres, also known as “cough phases”. These phases are the deep inspiratory phase, compression phase (glottic closure), expulsion phase, and recovery phase (Nadel, Murray et al. 2000). The first phase of the cough consists of deep inspiration through the open glottis. This deep inhalation varies from one subject to another and it usually provides a large lung volume (vital capacity), open airways in preparation for their clearance, and stretches the expiratory muscle. In the compressive phase, the glottis suddenly closes while the expiratory muscle contracts. This closure of the glottis increases the interpleural

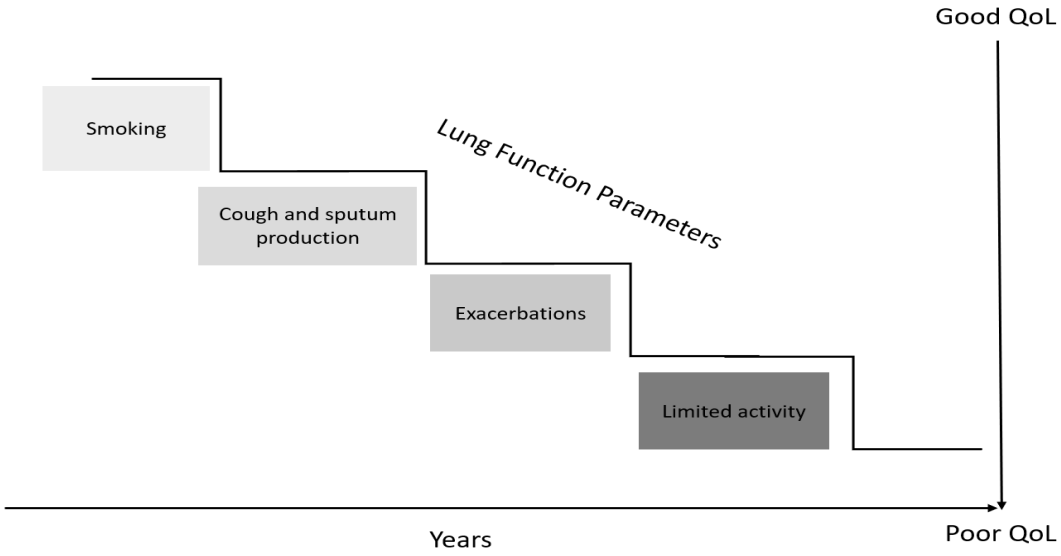
and interalveolar pressure up to 400 cmH2O. This phase mostly lasts for <200 milliseconds. The expulsive phase follows when the glottis opens, and air starts leaving the large airways. The expulsive phase has different presentations based on the amount of alveolar pressure that enters the lungs, as well as the interruption of the open glottis. In the expulsive phase, a cough sound is made as a result of air and sputum leaving the large airways as the glottis closes. The cough ends with the recovery or restorative phase where the lungs restore the tidal volume that was reduced during the expulsive phase (Chung, Widdicombe et al. 2003).

1.7 Causes of coughing and sputum production in COPD

Coughing and sputum production are often the first symptoms of COPD and are present in 30% of the COPD population (GOLD 2021). They appear intermediately in the early stages of the disease and increase in severity as the disease progresses (Van Schayck, Loozen et al. 2002). Smoking is by far the most significant cause of coughing and sputum production in COPD; however, other reasons have also been reported in the literature (Figure 1.4). They can cause an acute or chronic cough. First, a substantial inflammation profile in the airways and lung tissues is associated with coughing and sputum production (Bhowmik, Seemungal et al. 2000, Rutgers, Postma et al. 2000, Contoli, Baraldo et al. 2020). A cough can also be induced by accumulation of sputum in the small airways due to impaired mucociliary clearance function (Hogg, Chu et al. 2004). Acute exacerbation is strongly associated with coughing and sputum production in COPD (Vestbo 2002, Burgel, Nesme-Meyer et al. 2009). Finally, viral respiratory infections (i.e. COVID-19) and other comorbidities (i.e. gastroesophageal reflux and bronchiectasis) can contribute to the onset, frequency and the severity of the cough in COPD patients (Casanova, Baudet et al. 2004, Benson, Müllerová et al. 2015, Carfì, Bernabei et al. 2020). This is what we know so far, but

there is much to learn about productive and non-productive coughs with COPD patients and the related causes (Chung, Widdicombe et al. 2003).

Figure 1.4 COPD and significant factors contributed to decline in lung function and poor quality of life over the years.

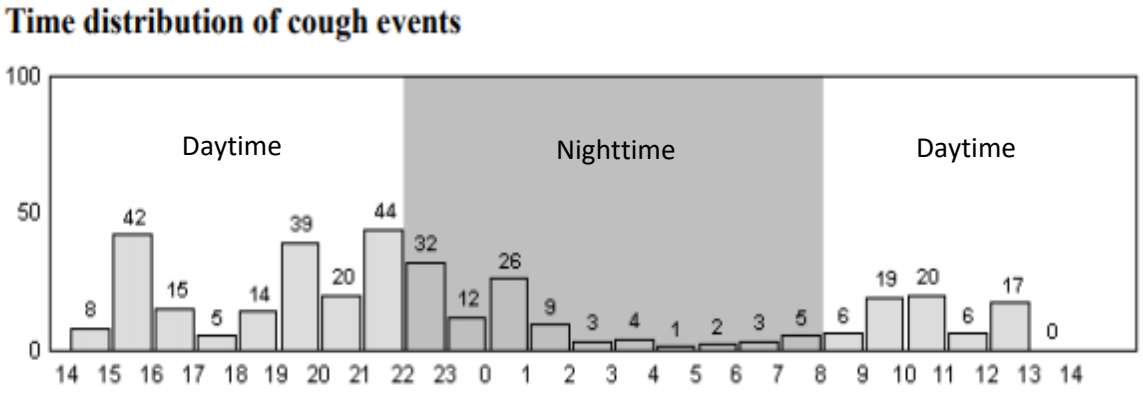


1.8 Daytime and nighttime cough with COPD

Coughing in COPD patients is different in the morning and at night. During the sleep, the cough can cause more frequent waking. This is common with COPD and its impact is reflected in the limitations on daytime activity, contributing to sleepiness and fatigue during the daytime (Kinsman, Yaroush et al. 1983, Lange, Marott et al. 2014). Coughing and sputum production in the early morning are a hallmark of COPD patients with chronic bronchitis (Roche, Small et al. 2013). A strong, productive cough in the morning occurs to clear accumulated secretions overnight. Daytime and nighttime coughs can be impacted by many factors. So far, clinical research shows that smoking status, mucus accumulation, and certain drugs are associated with

higher cough characteristics in the night (Lee and Birring 2010, Fischer, Gross et al. 2018). Sleep disturbance caused by coughing and sputum production was associated with worse COPD clinical outcomes, including exacerbations, health care utilization, and mortality (Omachi, Blanc et al. 2012, McNicholas, Verbraecken et al. 2013). There is much to learn about the mechanism behind the cough behaviours of chronic bronchitis patients and the relationship between nighttime cough and daytime symptoms. Figure 1.5

Figure 1.5 A 24-hours cough counting in patient with COPD with frequent cough and sputum production. Gray zone indicated the night-time cough event.

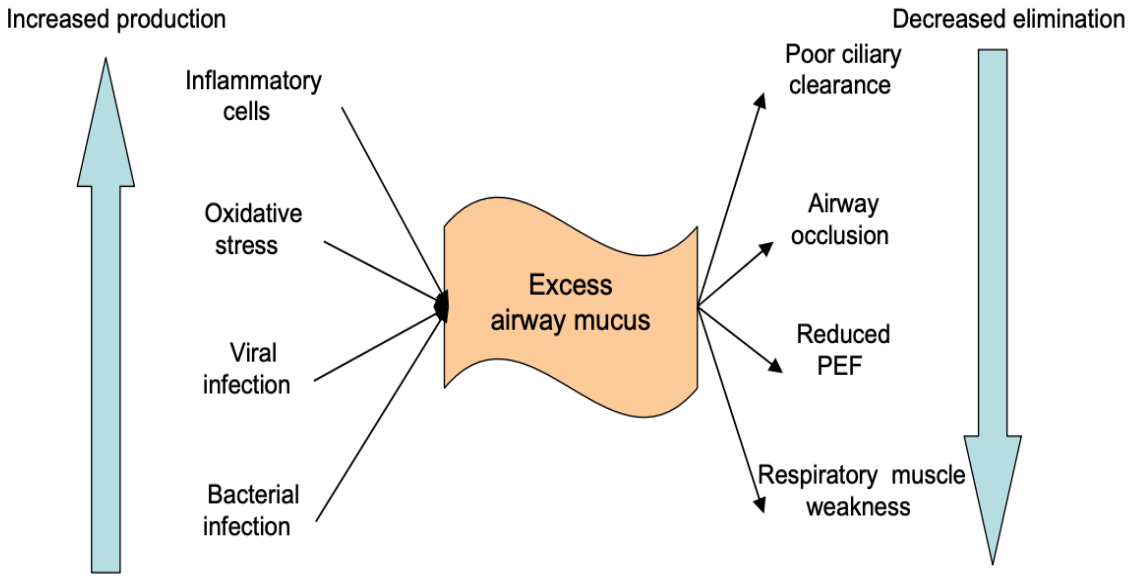


1.9 Mucus hypersecretion

COPD with a persistent productive cough daily or most days of the week is commonly seen in clinical settings (Kesten and Chapman 1993, Barker, Laverty et al. 2017). A productive cough with COPD is also considered an indicator of excessive mucus secretion in both the large and small airways. Normally, airway lumen is covered by a thin layer of viscoelastic liquid to protect the epithelium surface from damage and dehydration (Widdicombe and Widdicombe 1995). This viscoelastic liquid is called “mucus” and is a complex mixture of water, proteins, enzymes,

electrolytes, lipids, and other cellular mediators. The mucus, which is located at the top of ciliated cells, works as an escalator to remove inhaled particles. This mechanism is called mucociliary clearance (Wanner, Salathé et al. 1996, Wiley 2001). In the context of COPD, mucus hypersecretion is mostly defined by increased mucus production as well as mucociliary dysfunction against inhaled irritants or gases (Rogers 2007). When mucociliary functions are impaired, a cough occurs. It can be acute, as in acute exacerbations, or chronic, as in chronic bronchitis and smokers. Figure 1.6

Figure 1.6 Possible causes and complications of mucus accumulation in individuals with COPD (Ramose et al., 2014).



1.9.1 Components of mucus

Mucus consists of 98% water particles, which are bound with a viscoelastic gel containing mucins (Knowles and Boucher 2002, Kesimer, Ford et al. 2017). Mucins (MUC) are heavy glycoproteins produced by the submucosal glands and goblet cells in the bronchial wall and epithelium surface. They are markers for mucus hypersecretion in COPD. Mucins provide the viscoelastic properties to help in mucociliary clearance and mucus transport (Litt, Khan et al. 1974). To date, more than 19 mucins have been discovered, of which two are predominantly found in patients with chronic bronchitis: MUC5B and MUC5AC (Kesimer, Ford et al. 2017). Both mucins contribute to forming the gel phase and viscoelasticity properties of the mucus. A higher concentration of mucins contributes to poor viscoelasticity of the mucus, and therefore reduced mucociliary clearance (Kesimer, Ford et al. 2017).

1.9.2 Measurements to quantify sputum

There is a lack of references for quantifying sputum in COPD, unlike other chronic respiratory disease (Franks, Walsh et al. 2020). To date, there has been no systematic review or meta-analysis comparing the clinical measurements of sputum production in the COPD population. However, laboratory studies have advanced to evaluate the characteristics and descriptions of mucus in COPD, including identifying the biomarkers of the mucus (MUC5AC), the biophysical properties of the phlegm, and the number and size of the cells or tissues (Voynow and Rubin 2009). In clinical studies, there are different measurements to report outcomes related to sputum expectoration, using grams, millilitres, tablespoons, wet sputum weight, colour, and frequency. Questionnaires are also used to report sputum production (this will be discussed in chapter 3). All have been used previously in clinical practice. It is important to mention that there is still a lack of literature

on a simple, valid, reliable measurement to quantify sputum clearance. Examples of sputum measurements from selected clinical studies on COPD are reported in Table 1.2.

Table 1.2 Examples of sputum measurements in the literature.

Subjects	Sputum measurements; reference
Chronic bronchitis	Sputum cell counts (eosinophiles and macrophages); (Gibson, Girgis-Gabardo et al. 1989).
Chronic bronchitis	Radioactive aerosol tracer technique; (Van der Schans, Piers et al. 1990).
Chronic bronchitis	Sputum wet weight in grams; (Bellone, Lascioli et al. 2000).
Chronic bronchitis	Total amount of sputum per day in grams; (Bellone, Spagnolatti et al. 2002).
COPD with exacerbations	Sputum colour (none or white, yellow, green, brown), Sputum quantity (tablespoons), Sputum consistency (none, watery, thin, thick; (Krahnke, Grabianowski et al. 2011).
Chronic bronchitis with exacerbations	Sputum culture and sputum bacteria; (Miravitlles, Kruesmann et al. 2012).
COPD	Wet sputum volume in grams; (Gastaldi, Paredi et al. 2015).
COPD with exacerbations	Sputum volume of more than one tablespoon (15 ml) per day; (Milan, Bondalapati et al. 2019).

Note: COPD, chronic obstructive e pulmonary disease; ml, millilitre

1.10 How sputum is closely associated with coughing in Chronic Bronchitis

The terms mucus and sputum are using interchangeably to describe the expectorants from the respiratory system in chronic bronchitis (Burgel 2012). In 1954, Reid discovered the relationship between excess mucus secretion in the airways and COPD (Reid 1954). Gradually, researchers discovered that sputum production is mostly assisted by coughing and it appears predominantly with smoking or in the early stages of smoking cessation (Fletcher and Peto 1977, Mullen, Wright et al. 1987, Lange, Groth et al. 1989).

In the context of COPD, chronic inflammation in the epithelium and airways, inflammation markers, submucosal gland hypertrophy and hyperplasia, goblet cell metaplasia, and oxidants derived from smoking contribute to mucus overproduction (Sommerhoff, Nadel et al. 1990, Degroote, Maes et al. 2003, Hogg, Chu et al. 2004, Shao, Nakanaga et al. 2004). Together with ciliary function abnormalities, these increase the amount of neutrophil elastase, the likelihood of premature airway collapse, and structural changes in the lung (Kinsman, Yaroush et al. 1983). Altogether, the result is an accumulation of mucus in the large airways covered by cough receptors that stimulate coughing (Thurlbeck 1990). The cough is the predominant mechanism to clear accumulated excess mucus in the airways in the form of a productive cough. If the mucociliary functions and cough fail and become ineffective, the airways may be persistently plugged, which increases over time, causing severe airway obstruction (Nadel 2013).

1.11 Coughing and sputum production as risk factors for poor clinical outcomes

Coughing and sputum production have been suggested in several clinical studies as risk factors for poor outcomes, such as a decline in lung function, poor quality of life, frequent exacerbations, fatigue, poor physical activity, sleep deprivation and mortality rate (Miravitlles 2011, Ramos, Krahnke et al. 2014). Table 1.3 summarises some of the evidence.

Table 1.3 Summary for clinical outcomes in chronic bronchitis.

Clinical outcome	Key Findings; Reference
Health quality of life	CB is related to poor health-related quality of life in COPD grades; (Agusti, Calverley et al. 2010, Kim, Han et al. 2011).
Frequent exacerbations	CB is related to an increase in the number of exacerbations and hospitalisations in all COPD grades; (Burgel, Nesme-Meyer et al. 2009, Agusti, Calverley et al. 2010, Kim, Han et al. 2011, de Oca, Halbert et al. 2012)

Deterioration in lung function	CB results in a decline in FEV1 and FEV1/FVC ratio; (Sherman, Xu et al. 1992, Lindberg, Eriksson et al. 2006, De Marco, Accordini et al. 2007, Kim, Han et al. 2011).
Physical activity	CB is related to muscle wasting and limitations of day-to-day physical activity; (Baghai-Ravary, Quint et al. 2009, Kanervisto, Saarelainen et al. 2010, Shrikrishna, Patel et al. 2012, Donaire-Gonzalez, Gimeno-Santos et al. 2013)
Fatigue	CB is related to an increase in fatigue outcomes; (Kinsman, Yaroush et al. 1983, Baghai-Ravary, Quint et al. 2009, Goërtz, Spruit et al. 2019).
Sleep efficiency	CB is related to sleep disturbance and poor sleep quality; (Kinsman, Yaroush et al. 1983, Hartman, Prinzen et al. 2015, Donovan, Rise et al. 2017, Spina, Spruit et al. 2017)
Mortality	Cough and sputum production are related to the causes of death in patients with COPD with or without exacerbations; (Annesi and Kauffmann 1986, Speizer, Fay et al. 1989, Prescott, Lange et al. 1995).

Note: CB, chronic bronchitis

1.12 Cough and sputum production in AECOPD

Exacerbations of COPD are associated with increased airway inflammation as well as systemic inflammation (Burge and Wedzicha 2003). In the COPD population, those with frequent exacerbations have worse health status and faster disease progression than those with infrequent exacerbations (Hurst, Vestbo et al. 2010). COPD exacerbations are often caused by bacteria and viral infections. (Sethi 2000, Sethi 2004, Wedzicha and Seemungal 2007). These infections impair the small airways' defence mechanisms, resulting in epithelial cell damage, impaired mucociliary clearance, and inflammatory cell infiltration, causing more mucus production (Murphy and Sethi 1992, Wedzicha 2004).

1.13 Current therapies for excessive coughing and sputum production

Treatment for COPD must take into consideration comprehensive management because COPD is mostly a combination of comorbidities, and it is heterogenous from one patient to another. Smoking cessation, pulmonary rehabilitation programmes and exercises are considered key components of COPD management. Treating one aspect, such as sputum accumulation, will contribute to managing the disease, but attention must be given to other underlying problems, which should receive the same care. In the management of COPD, it is important to reverse the mucociliary functions and treat sputum production to prevent the negative impact of sputum accumulation on the overall clinical outcome. Smoking cessation is at the top of these therapies, the aim of which is to reduce sputum production by controlling inflammation in the lungs and facilitating mucus expectoration. These therapies can be applied to both stable and non-stable COPD (with exacerbations) and can be classified as pharmacological and non-pharmacological therapies.

1.14 Smoking cessation

Quitting all types of smoking has been found to be effective in improving the reversibility of the impaired mucociliary clearance that is damaged by tobacco smoking and oxidative agents as well as it helps to slower the decline in lung function (Anthonisen, Connett et al. 1994, Anthonisen, Connett et al. 2002, Cipulo Ramos, De Toledo et al. 2011). Willemse et al. looked at the impact of smoking cessation for one year in COPD smokers. The study methodology included taking bronchial biopsies at the baseline and 12 months later. The researchers found that quitting smoking for one year successfully reduced inflammation as well as the number of sputum cells (i.e. macrophages and eosinophils) (Willemse, ten Hacken et al. 2005).

1.15 Pharmacological therapies for sputum clearance

Inhalation and oral mucolytic therapies are also used to reduce the burden of sputum accumulation and improve sputum expectoration in COPD patients with coughing and sputum production (McCrory and Brown 2003, Balsamo, Lanata et al. 2010, O'Reilly, Jones et al. 2010). For COPD, bronchodilators and inhaled steroids are commonly used treatments. Mucoactive drugs that have been used in clinical practice include expectorants, mucolytics, mucoregulators, and mucokinetics. Each mucoactive drug has a potential mechanism (Balsamo, Lanata et al. 2010). However, action and efficacy of most medications is controversial and lack of robust clinical evidence. The summary table below (Table 1.4) provides some examples of medications that have been used in clinical settings and the mechanism of their actions.

Table 1.4 Summary of the pharmacological therapies for sputum clearance.

Drug name	Examples	Potential mechanism; Reference
Bronchodilators	Tiotropium Salmeterol	Improve airflow during the cough. Improve smooth muscle relaxation; (Barnes 1995, Tashkin and Cooper 2004, Barker, Laverty et al. 2017)
Expectorants	Hypertonic saline Guaifenesin	Increase secretion hydration and/or reduces viscosity; (Ohar, Donohue et al. 2019, Bennett, Henderson et al. 2020)
Mucoregulators	Carbocisteine	Modulate mucus production cells and/ or decrease mucus volume; (Zheng, Kang et al. 2008)
Anti-inflammatories and antibiotics	Anticholinergic agents Glucocorticoids Macrolide antibiotics	Reduce airway inflammation; (Gross 1987, Mapp 2000, Siempos, Dimopoulos et al. 2007)
Mucolytics	N-Acetylcysteine	Break the bonds between mucin polymers and/ or work as antioxidants; (Stey, Steurer et al. 2000, Cazzola, Calzetta et al. 2018)
Mucokinetics	Surfactant	Improve mucus transport by decreasing the sputum adhesive. (Kory, Hirsch et al. 1968, Anzueto, Jubran et al. 1997)

1.16 Non-pharmacological therapies for sputum clearance

Non-pharmacological therapies, such as airway clearance techniques, are also used to aid airway clearance in COPD patients. These therapies can be done independently by the patient, or the patient can be assisted by a physiotherapist or an adjunct device. Independent techniques, such as breathing exercises, rely on the extent to which the patients can perform the exercise as well as their cognitive ability to perform it effectively. On the other hand, techniques such as postural drainage and sputum clearance devices rely on the feasibility of the technique and /or functionality of the devices and their ability to help in clearing the secretions. All therapies are intended to mobilise accumulated secretions from the distal airways to the central airway and to increase lung volume and airway flow to help in sputum evacuation (Volsko 2013).

In COPD patients who experience frequent sputum production, mucus accumulation can occlude the small airways, which consequently worsens the V/Q mismatch, increases hypoxia and the work of breathing, and contributes to microatelectasis (O'donnell and Laveneziana 2006). Failure to clear the accumulated sputum may result in its colonisation by pathogenic organisms that can exacerbate the disease's symptoms. Thus, airway clearance is an important health goal, and airway clearance techniques (ACTs) are currently used to treat sputum production in COPD patients (Barker, Laverty et al. 2017, Bourbeau, McIvor et al. 2019).

ACTs, such as percussion, vibration, and deep breathing, can be used to treat patients with COPD. Depending on the disease severity and clinical manifestations, an ACT can be considered part of the management plan for patients with COPD (Spiro, Silvestri et al. 2012) on the basis that the

maintenance of airway function using airway clearance therapy should help patients with COPD mobilise and eliminate accumulated mucus, prevent mucus retention, reduce the risk of infection, reduce clinical symptoms, improve lung mechanics, and promote gas exchange (Myers 2007, Barker, Laverty et al. 2017, Bourbeau, McIvor et al. 2019). It is important to mentioned that in chronic lung diseases such as bronchiectasis, modalities for airway clearance are often prescribed bedside the pharmacological interventions (Lee, Burge et al. 2015). Various ACTs are clinically prescribed for patients with COPD (Volsko 2013).

1.17 Airway clearance techniques (ACTs)

1.17.1 Independent techniques

1.17.1.1 Coughing exercise

The coughing exercise is the body's frontline reaction to clear sputum in COPD patients. Coughing in patients with COPD may be ineffective because of loss of elasticity of the lung parenchyma, which can lead to airway collapse during forced expiratory manoeuvres and is indicative of trapped air and sputum in the lung periphery (Egan, Sheldon et al. 1982). Van der Schans et al. evaluated coughing and sputum production in chronic bronchitis and emphysema. The research found that coughing can enhance mucus clearance in chronic bronchitis but not in emphysema patients. The mean mucus clearance with cough was greater than forced expiration and huffing exercises (Van der Schans, Piers et al. 1990). Bellone et al. evaluated the impact of adding assisted cough techniques to non-invasive positive pressure ventilation (NIPPV) for COPD patients with acute exacerbations versus assisted cough alone. This study found that adding assisted cough to NIPPV helped with mucus secretion and faster weaning from NIPPV.(Bellone, Spagnolatti et al. 2002) In chest physiotherapy for COPD, cough exercises and assisted cough (manually or with

devices) are key components in airway clearance therapy. The cough reflex can be difficult or diminished in people with neuromuscular disease, chest deformities or those under sedation (Birring and Spinou 2015).

1.17.1.2 Active cycle of breathing techniques (ACBT)

First described by Pryor et al. in 1979 (Pryor, Webber et al. 1979), this is a sequence of breathing techniques that help in loosening sputum. This technique starts with controlled breathing, followed by deep breathing held for a couple of seconds (generally 3–5 seconds), and ends with the forced expiration technique (FET). This technique must be done in a cycle of these three modes of breathings. The technique takes approximately 15 minutes and each sequence of breathing can be adapted based on the individual's needs. Previous clinical trials with COPD have suggested that the technique produces improvements in daily airway clearance, lung function parameters, physical activity, and oxygen saturation (Cecins, Jenkins et al. 1999, Savci, Ince et al. 2000). Systematic reviews and meta-analysis have shown that this is beneficial in sputum removal for patients with COPD (Ides, Vissers et al. 2011, Lewis, Williams et al. 2012, Shen, Li et al. 2020, Zisi, Chryssanthopoulos et al. 2022). In 2018, NICE guidelines added ACBT as part of the usual care for people with COPD under section 1.2.99 (Hopkinson, Molyneux et al. 2019).

1.17.1.3 Autogenic drainage (AD)

This was first discovered by Jean Chevaillier in 1967 (Chevaillier 2016) and described by Dab & Alexander in 1979 (Dab and Alexander 1979). Unlike ACBT, AD is a breathing technique performed in three phases and it includes three breathing patterns. The first phase is "unstick", where the patient must breathe at a low volume (shallow breaths) to speed the expiratory flow and reduce adhesion of the mucus. The second phase is "collect", where the patient must

increase the breathing to mid-tidal volume to help create a shear force in the bronchial wall and collect the mucus into the central airways. The third phase is “evacuate”, where the patient needs to take a series of large breaths to encourage a spontaneous cough to expectorate the phlegm (Dab and Alexander 1979). This technique takes approximately 20 minutes and each phase duration depends on the individual’s needs. This technique has been found to be effective with diseases such as cystic and non-cystic fibrosis lung conditions (Morgan, Osterling et al. 2015). In the context of COPD, there are few studies investigating the effect of AD on airway clearance; however, it seems promising for improving lung function parameters (i.e. VC, FEV1, and PEF), oxygen saturation, and physical activity measured with the six-minute walk test (Savci, Ince et al. 2000, Jahan, Kumar et al. 2015).

1.17.1.4 Expiration with glottis opened in lateral posture (ELTGOL)

This technique involves using spontaneous ventilation through the opened glottis to mobilise secretions in the lateral decubitus position on both lung sides with slow expiration manoeuvres (Kodric, Garuti et al. 2009). This airway clearance technique aims to control expiration flow and interrupt premature closure of the airways, and then stimulate a cough (Milibari 2018). This technique is mostly used in mild to moderate COPD and is effective at increasing mucus clearance (Martins, Andrade et al. 2006, Kodric, Garuti et al. 2009, Martins, de Andrade et al. 2012).

1.17.2 Semi-dependent techniques/manual techniques

1.17.2.1 Postural drainage (PD)

This technique uses the position of the body as well as gravity to facilitate moving accumulated secretions from the peripheral airways to the central airways (Pryor 1999). It is usually performed in the morning because secretions generally accumulate overnight. Unlike the previous airway

clearance techniques, PD requires expert physiotherapy. It basically involves positioning the area that needs to be drained higher than the main bronchi with attention paid to the lung structure. Drainage can take up to 10 minutes each side, depending on how much the area is filled with secretions. However, this technique should be used with caution because of its side effects (Hough 2001). Additionally, there is a lack of evidence for the clinical application of PD to COPD patients to aid sputum clearance compared to other techniques (Mohsenifar, Rosenberg et al. 1985, Olseni, Midgren et al. 1994, Bellone, Lascioli et al. 2000, Virendersingh, Khandelwal et al. 2003), especially with excessive sputum producers. The technique is also difficult for older people, it takes a longer time, and it may cause arrhythmia and desaturation in patients with COPD (Ides, Vissers et al. 2011).

1.17.2.2 Clapping, percussion, and vibrations

These manual techniques, used with or without PD, are applied to the chest wall to break down the secretions and help the patient to cough them up. Clapping or percussion refer to gentle rhythmic strikes on the chest wall using cupped hands or any mechanical means (i.e. percussors). Vibration involves applying hand vibrations to the chest wall while the patient performs prolonged expiration. Clinical studies have found that clapping and percussion are ineffective and associated with oxygen desaturation and airflow obstructions in CB (Campbell, O'CONNELL et al. 1975, Connors Jr, Hammon et al. 1980, Wollmer, Ursing et al. 1985).

1.17.3 Device-dependent techniques

1.17.3.1 Positive expiratory pressure (PEP) devices

PEP therapy uses an interface device, such as a mask or mouthpiece, and involves exhaling against resistance flow to produce back pressure in the airways. Usually, PEP devices incorporate

a manometer to monitor expiration pressure as well as an orifice and/or valve to resist exhalation. The aim of this device is to create a pressure gradient to allow airflow in the peripheral airways through collateral ventilation behind the retained secretions, and thus move secretions toward the central airways where evacuation occurs (Van Der Schans, van der Mark et al. 1991). The effectiveness of the PEP therapy is dependent on the position of the patient, the extent to which the mask is close-fitting, air leakage, and controlled expiration (between 10 to 15 cmH2O) (Myers 2007). PEP therapy is a useful therapy for sputum clearance. It has the same effect as ACBT in improving lung function parameters as well as physical activity (Su, Chiang et al. 2007). The small number of long-term studies that investigate the use of PEP masks with COPD patients suggest significant benefits in reducing the burden of the cough and sputum production, as well as a reduction in morbidity, slower decline in lung function (Christensen, Nedergaard et al. 1990), and reduced number of exacerbations and hospitalisations (Osadnik, McDonald et al. 2014, Nicolini, Mascardi et al. 2018). NICE guidelines recommend (article number 1.3.36) that PEP devices be used for acute exacerbations of COPD to aid airway clearance (AECOPD) (Hopkinson, Molyneux et al. 2019).

1.17.3.2 Temporary positive expiratory pressure (T-PEP)

T-PEP involves a set of two devices, including an electronic device to apply low PEP ~1 cmH2O during expiration and an oscillatory expiratory device (Lung Flute) to generate oscillations of around 18 to 22 Hz. The aim of the device is to keep the alveoli open as well as detach secretions from the airways (Nicolini, Mascardi et al. 2018). Nicolini and his colleagues found that T-PEP can reduce exacerbations of COPD in 26 weeks (Nicolini, Mascardi et al. 2018) and it has a positive impact on hospitalisations, (Mascardi, Grecchi et al. 2016) lung function parameters, and

dyspnoea symptoms (Nicolini, Mascardi et al. 2015). A retrospective study suggested that T-PEP and PEP are similarly helpful for improving gas exchange, and a great improvement was seen with emphysematous patients and/or patients on long-term oxygen therapy. However, there is a lack of evidence regarding this new technique for usual care and only a few clinical trials compare T-PEP to other treatments (Nicolini, Mascardi et al. 2015, Mascardi, Grecchi et al. 2016, Nicolini, Mascardi et al. 2018, Nicolini, Mascardi et al. 2018).

1.17.4 Other machine-dependent techniques

1.17.4.1 Non-invasive ventilation to improve airway clearance

Following the concept of applying PEP to the lungs, non-invasive mechanical ventilation (NIV) has joined the airway clearances techniques for patients with COPD; it was previously used mainly in cystic fibrosis patients (Moran, Bradley et al. 2017). Only one clinical study has reported the effectiveness of NIV in removing secretions with chronic bronchitis; however, this study was short-term and with a small number of patients (Bellone, Spagnolatti et al. 2002).

1.17.4.2 Intrapulmonary percussive ventilation (IPV)

An IPV device involves a high-pressure flow generator, valve for flow interruption, and face mask or mouthpiece connected to a breathing circuit. The concept of IPV is to deliver high-flow respiratory rate internal percussion bursts (50–650 cycles/min) using the Venturi principle. Together with interrupted airflow and gases during breathing, this promotes gas exchange and intrabronchial mobilisation of the secretions. Studies have shown that IPV can decrease diaphragm loading as well as the respiratory rate (Nava, Barbarito et al. 2006, Vargas and Hilbert 2006). It was also found to decrease hospitalisations of patients with AECOPD (Vargas and Hilbert

2006). There is limited knowledge available about IPV use in COPD patients to promote airway clearance.

1.17.4.3 Mechanical insufflation/exsufflation and CoughAssist

Mechanical insufflation/exsufflation uses maximum lung inhalation during inspirations and then an abrupt switch to negative pressure to the upper airways during expiration to stimulate airflow changes during the cough process. This device is also known as CoughAssist (Kacmarek, Stoller et al. 2019). Few studies have found this device effective in the subset of COPD patients who suffered from neuromuscular disease (Sivasothy, Brown et al. 2001, Winck, Gonçalves et al. 2004). The same prospective clinical trial failed to report any impact on airway clearance in patients with COPD without neuromuscular disease (Sivasothy, Brown et al. 2001, Winck, Gonçalves et al. 2004).

1.17.4.4 High frequency chest wall compression (HFCWC)

High-frequency chest wall compression is administered using a jacket or vest around the chest wall. This device aims to apply high-frequency oscillations via the jackets to the external surface of the thorax to increase mucus-airflow interactions and decrease mucus viscosity (Hansen, Warwick et al. 1994, Tomkiewicz, Biviji et al. 1994, Dosman and Jones 2005). A pilot clinical study using HFCWC for COPD reported potential benefits in airway clearance, COPD symptoms, and quality of life (Chakravorty, Chahal et al. 2011). Another randomised clinical trial done by Nicolini and his team showed that using HFCWC for four weeks can improve health status and overall COPD symptoms (Nicolini, Grecchi et al. 2018). However, HFCWC is still not widely used in clinical settings with COPD patients.

1.17.5 Oscillatory positive expiratory pressure (OPEP)

One ACT involves the use of adjunct sputum clearance devices, such as oscillatory positive expiratory pressure (OPEP) devices. These devices mechanically interrupt the expiratory flow with different frequencies.(Alghamdi, Barker et al. 2020) These frequencies generate shearing forces that reduce the viscoelasticity of secretions and improve mucus transport. The use of OPEP devices is intended to help patients with COPD clear the produced sputum from their chest; however, there is limited data regarding their effectiveness, which leads to uncertainty about the indications for their use (Barker, Laverty et al. 2017, Bourbeau, McIvor et al. 2019, Alghamdi, Barker et al. 2020, Daynes, Jones et al. 2021). Therefore, OPEP devices are not mentioned in the clinical guidelines for the management of COPD. Systematic reviews and meta-analyses on the use of hand-held OPEP devices show that they may contribute to improving mucus clearance, reducing hospitalisations, improving short-term health status and quality of life, and promoting exercise tolerance (Bourbeau, McIvor et al. 2019, Alghamdi, Barker et al. 2020, Daynes, Jones et al. 2021). However, these findings are based on a limited number of trials involving a small number of participants. Currently, there are different hand-held OPEP devices that are used to aid mucus clearance.

1.17.5.1 Flutter

The Flutter is a hand-held, pipe-shaped device with a mouthpiece. Inside the pipe and in the rest of the circular cone, there is a stainless-steel ball. During exhalation, the ball moves up and down, interrupting expiration and creating PEP ranging between 17 and 35 cmH2O with frequencies in the range 8–26 Hz (Weiner, Zamir et al. 1996). The patient must be sitting in an upright position to use the Flutter. Clinical studies of COPD have shown that the Flutter, postural drainage, and

breathing exercises significantly increase sputum expectoration; however, the difference between these three methods was not significant (Ambrosino, Callegari et al. 1995, Bellone, Lascioli et al. 2000) Figure 1.7.

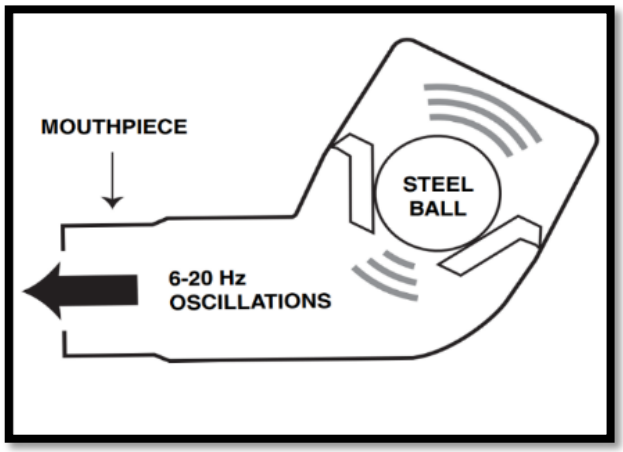


Figure 1.7 Flutter device (Flutter; Axcan Scandipharm, USA) (Wolkove, Baltzan et al. 2004).

1.17.5.2 RC-Cornet

The RC-Cornet is a curved hose device consisting of a valve and mouthpiece. It follows the same physiological principles of the Flutter device. During expiration, the flow passes through the tube and the valve, creating oscillations in the airways (Cegla, Jost et al. 2002). A short-term clinical trial of the RC-Cornet for COPD showed that it is effective in improving dyspnoea and sputum clearance (Cegla, Bautz et al. 1997), and a long-term clinical trial showed that the RC-Cornet is effective in decreasing the need for antibiotics and improving lung function parameters (Cegla, Jost et al. 2002). It was also found useful for improving the deposition and bronchodilation effects in COPD (Cegla, Jost et al. 2001, Haidl, Rickert et al. 2002). In COPD patients, fewer studies have assessed whether RC-Cornet impacts clinical outcomes (Cegla, Bautz et al. 1997, Cegla, Jost et al. 2001, Haidl, Rickert et al. 2002) (Figure 1.8).

Figure 1.8 RC-Cornet (Cegla RC-Cornet; Oxegio, Germany)(Cegla, Jost et al. 2002).

1.17.5.3 Lung Flute

Unlike other OPEP devices, the Lung Flute has a different mechanism of action. It uses acaustic waves to generate oscillations during expiration, which range from 16 to 22 Hz and travel down to the airways (Sethi, Yin et al. 2014). The device is safe to use with COPD, but a long-term clinical trial showed that the Lung Flute is the same as ACBT in terms of improving overall COPD symptoms and airway clearance (Sethi, Yin et al. 2014). Unpublished data show that the Lung Flute has the same impact as the Acapella in improving sputum clearance and quality of life in CB patients (Sethi, Maloney et al. 2018) (Figure 1.9).

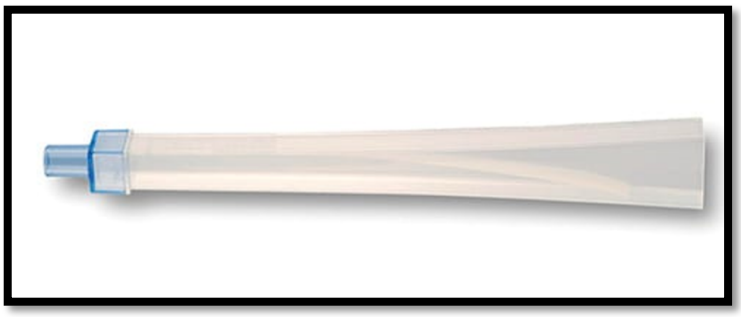


Figure 1.9 Lung Flute (Medical Acoustics, Buffalo, NY) (Nicolini, Mascardi et al. 2018).

1.17.5.4 Acapella choice

The Acapella is a hand-held, flow-operated device consisting of a counterweighted plug and magnet as well as mouthpiece. During expiration, the flow passes the plug, creating oscillations that move down to the airways. The Acapella has a knob to adjust the flow resistance and frequency of oscillations. The device is not gravity-dependent, so the patient can use the device in any position. It comes in two models: the blue model (if the patient has expiratory flow >15 L/min) and green model (if the expiratory flow <15 L/min). Compared to the Flutter device, the Acapella produces more oscillations in the lower airways due to flexibility in adjusting the flow pressure. It is also simple and easy to use, especially for patients who cannot generate forceful expiration due to severe airway obstruction (Volsko, DiFiore et al. 2003). In COPD patients, adding the Acapella device to pulmonary rehabilitation was found to be useful in improving sputum clearance and exercise capacity (McCarroll 2005). However, there is only one available clinical trial evaluating the impact of adding Acapella to usual care or usual care alone; this clinical trial found the Acapella effective in reducing the hospital stay (Milan, Bondalapati et al. 2019) (Figure 1.10).

Figure 1.10 Acapella device (Smiths medical; Portex, USA)(Flume 2003).

1.17.5.5 Aerobika

The Aerobika is a member of the OPEP family. It consist of a proprietary pressure oscillation dynamo to generate the PEP during expiration (Tse, Wada et al. 2020). Adding the Aerobika to the usual care has shown effectiveness in reducing the rate of severe exacerbations and hospital admissions compared to the Acapella (Tse, Wada et al. 2020). Aerobika was found to be effective in sputum clearance, reducing COPD symptoms, improving health status and physical activity. However, the study size was small and it lacked a control (Svenningsen, Paulin et al. 2016). Audit review studies show that adding the Aerobika to the usual care produces positive economic and clinical outcomes (Burudpakdee, Seetasith et al. 2017, Khoudigian-Sinani, Kowal et al. 2017) (Figure 1.11).

Figure 1.11 Aerobika (Trudell Co.; Canada) (Suggett, Meyer et al. 2014).

1.17.5.6 Aerosure

Unlike previous OPEPs, the Aerosure is a battery-operated device with a mouthpiece. The mechanism of the Aerosure is based on airflow velocity and resistance during inspiration and expiration. It is also called a high-frequency airway oscillating (HFAO) device. The patient can use the device for inhalation and exhalation. During inhalation, the Aerosure creates resistance ranging from 0 to 50 cmH2O, which helps the patient with inspiratory muscle training. During expiration, the device generates oscillations at either 15 or 25 Hz, which aids in mucus clearance. The resistance as well as the oscillations depend on the flow rate generated by the patient. To the best of our knowledge, only one pilot study has evaluated the impact of the Aerosure versus sham Aerosure devices on patients with COPD. This study found that the Aerosure is safe and effective for use with COPD, and it can help improve COPD symptoms and inspiratory muscles

(Daynes, Greening et al. 2021). In summary, there is little available about the safety and effectiveness of the Aerosure with COPD (Figure 1.12).

Figure 1.12 Aerosure device (Reviative Aerosure Medic; UK) (Daynes, Greening et al. 2022).

1.17.5.7 Bubble PEP set-up

Bubble-PEPs, or bottle-PEPs, consist of a plastic bottle filled with water and a breathing tube. To produce oscillations during expiration, the patient must breathe through the tube against a certain amount of water (usually 10 cm to produce 10 cm H2O). The amount of water in the bottle is reflected in the positive pressure (bubble) generated. Increasing the amount of water will increase the positive pressure (Mestriner, Fernandes et al. 2009). To perform this technique, the patient must be seated. The set-up device is safe and practical for use mostly in home pulmonary rehabilitation and/or clinical wards, but scant evidence supports its effectiveness in reducing sputum production in COPD (Eastwood, Jepsen et al. 2016, Keniş-Coşkun, Kocakaya et al. 2022)

Figure 1.13. Bubble PEP set-up (Eastwood, Jepsen et al. 2016).

1.18 Current knowledge gap

To the best of my knowledge, supported by the recent systematic reviews and meta-analyses that I have presented in chapter 3 (Alghamdi, Barker et al. 2020, Daynes, Jones et al. 2021), the use of OPEP devices is associated with improvements in sputum clearance, enhanced exercise capacity, decreased COPD symptoms, reduced exacerbation rate and hospital stay, and improved health status as well as overall quality of life. Unfortunately, assessment of the effect of OPEP devices is so far based on short-term studies with low-grade evidence and there is a lack of information regarding their long-term impact and effectiveness. Additionally, the efficacy of OPEP devices in treating COPD may be attributed to the general attitude of people toward using OPEP devices. For example, from 2013 to 2015, the prescription data in the UK indicated a high preference for prescription medications (i.e. carbocisteine and tiotropium) to treat patients with COPD in whom sputum production was a major complication. However, only a small number of patients with COPD who exhibited sputum production were treated with OPEP devices during

the same period (Barker, Laverty et al. 2017). Surveys have also shown variations between patients' and clinicians' preferences for using OPEP devices for sputum clearance (Barker, Laverty et al. 2017) (Figure 1.14). The extent to which long-term use of OPEP devices can help improve cough and sputum clearance, as well as health-related quality of life for patients with COPD, are important research questions, and it needs to be clearly understood whether they have a positive impact on patients' clinical outcomes or not. Ongoing mucus hypersecretions overnight could potentially impact the sleep quality of patients with COPD and whether those individuals have more, or fewer cough counts due to mucus hypersecretion. The aforementioned questions have been poorly investigated in the clinical research. A deep understanding of the impact of OPEP devices and all factors related to OPEP devices in the treatment of people with COPD can contribute to implementing effective interventions in the care plan for this population.

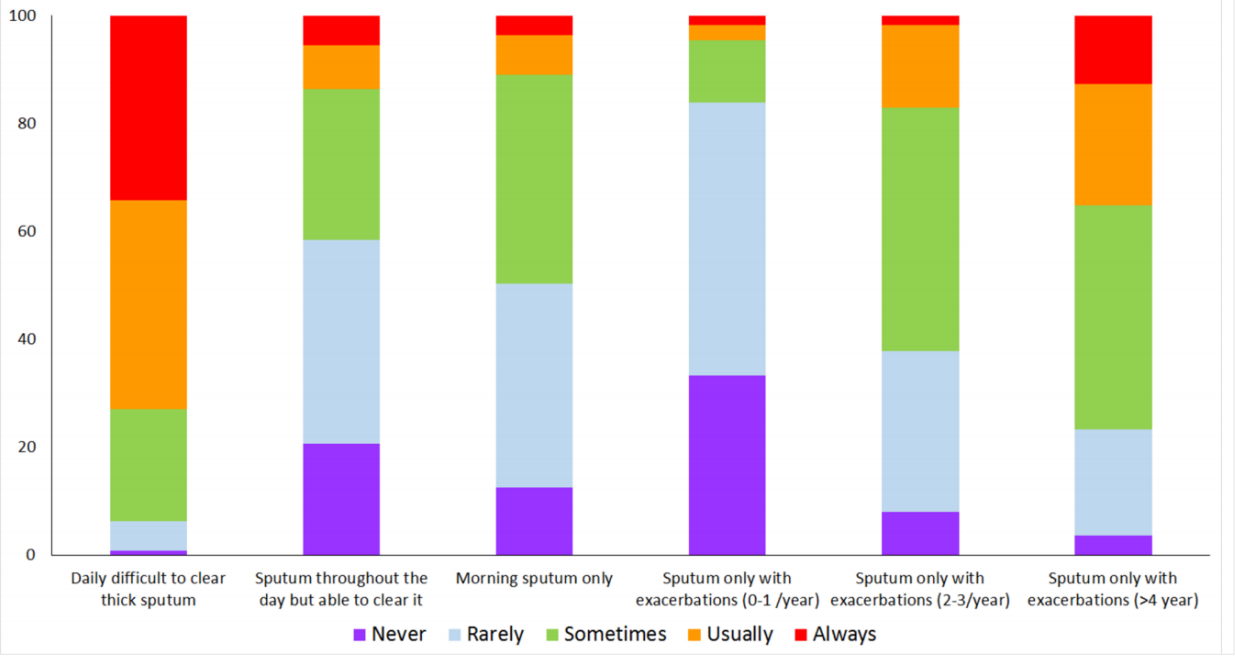


Figure 1.14 Data from Barker et al. study about how often would responders recommend oscillatory positive pressure devices for sputum clearance in a patient with this COPD (Barker, Laverty et al. 2017)

1.19 Thesis objectives

In this thesis, I have three main objectives. First, using accepted systematic review methodology to rigorously examine the current evidence on the use of OPEP devices for the treatment of cough and sputum clearance in patients with COPD who frequently produce sputum. Second, conduct a randomised clinical trial (acronym: O-COPD) to evaluate the impact of OPEP devices on the health-related quality of life in patients with COPD over a three-month time period. Third, evaluate the impact of OPEP devices on cough frequency and sleep actigraphy in a subset of the O-COPD group.

1.20 Aims of the projects and hypotheses

In this thesis, I had four main aims which are summarised as follows: The first aim was to use systematic review methodology to rigorously examine the current evidence on the use of OPEP therapy for cough and sputum clearance in patients with COPD who frequently produce sputum. The second aim was to conduct a randomised clinical trial (acronym: O-COPD) to evaluate the impact of OPEP therapy (Acapella) on the health-related quality of life over three-months in COPD who frequently produce sputum. The hypothesis is using OPEP device (Acapella) may improve cough-related quality of life compared to usual care. The third aim was to assess the correlation of objective cough frequency, sleep disturbance, and fatigue in people with COPD who frequently produce sputum. The hypothesis is cough frequency may correlate with sleep disturbance. The fourth aim was to evaluate the impact of OPEP therapy for three months on cough frequency and sleep disturbance in a subset of the O-COPD group. The hypothesis is using Acapella may reduce objective cough frequency and sleep disturbance compared to usual care.

2 Use of oscillatory positive expiratory pressure (OPEP) devices to augment sputum clearance in COPD: a systematic review and meta-analysis.

2.1 Abstract

Introduction: Oscillating positive expiratory pressure (OPEP) devices are intended to facilitate sputum clearance in COPD, but there is uncertainty as to their place in treatment pathways. We aimed to review the existing literature to establish the evidence base for their use.

Methods: A systematic search of records up to March 2020 was performed on PubMed, CINAHL, Medline (Ovid), Cochrane, and Embase to retrieve clinical trials that evaluated the efficacy of OPEP devices in patients with COPD. Two independent reviewers retrieved the titles, abstracts, and full texts, and completed the data extraction.

Results: Following full text review of 77 articles, 8 (six randomised control trials and two crossover studies) were eligible for inclusion. Pooled analysis showed that the use of OPEP devices was associated with decreased COPD symptoms and exacerbations (odds ratio [95% CI], 0.37 [0.19 to 0.72]), and enhanced exercise capacity; 6 minute walk distance (mean difference [95% CI], 49.8m [14.2m to 85.5m]; p=0.009]). However, studies were mostly short term with the majority having a high risk of bias. The average acceptance, completion, and dropout rates were 82%, 91%, and 8%, respectively.

Conclusion: The use of OPEP devices can have a positive impact in COPD, but effect sizes are generally modest and there is a need for further, higher quality studies to examine their long-

term efficacy in COPD as well as to identify specific patient phenotypes that are more likely to respond.

2.2 Introduction

In this published systematic review and meta-analysis I synthesised the available evidence regarding the effect of OPEP devices on outcomes including health-related quality of life (HRQoL) and symptoms of COPD, exacerbations of the disease, lung function, exercise capacity, antibiotic use, and hospital admission, as well as estimate the overall acceptance, completion, and dropout rates for clinical trials of OPEP devices in people with COPD to inform clinical practice and designing the O-COPD clinical trial (Chapter 4).

2.3 Methods

This systematic review was registered on PROSPERO (CRD 42016041835). The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guideline was used to complete this systematic review.

2.3.1 Inclusion criteria

1. *Study type*: randomised controlled and randomised crossover clinical trials.
2. *Population:* studies including individuals diagnosed with COPD (Defined as forced expiratory volume in 1 second (FEV_1)/ forced vital capacity (FVC) ratio <70%, and any history of smoking). Studies could be either in stable patients or at the time of AECOPD
3. *Type of intervention:* use of an OPEP device on its own or combined with another therapeutic intervention.

4. *Type of outcome:* All reported primary and secondary outcomes of COPD were extracted.

2.3.2 Exclusion criteria

1. Trials not translated or published in English.
2. Studies that did not include COPD patients or included a mixed population.
3. Studies that did not describe the type or frequency of the treatment.
4. Studies that evaluated the effect of OPEP devices in a single session of treatment only.
5. Studies that did not report the number of individuals who were approached for, consented to and completed the trial.

2.3.3 Search strategy

An electronic search of the following databases from earliest records to March 2020 was undertaken to identify and retrieve relevant articles: PubMed; CINAHL; MEDLINE (Ovid); Cochrane Library and Embase. Medical Subject Headings, subject headings, and/or keywords and combinations, used in all databases, were as follows: airway clearance device, airway clearance therapy; sputum clearance techniques, chest clearance techniques, Acapella, Aerobika, Flutter device, Lung Flute, positive expiratory pressure, positive expiratory pressure therapy, Oscillatory Positive Expiratory Pressure; OPEP; Chronic Obstructive Pulmonary Disease; Chronic Obstructive Lung Disease, and COPD. The search strategy was developed in collaboration with an expert health sciences librarian, to ensure the inclusion of appropriate and necessary keywords in the review. Keywords and subject terms were customised for each database. Full search strategy from all databases is provided in Appendix 4. Studies were defined as short-term if <12 weeks duration or long-term if $\geq$12 weeks.

2.3.4 Search procedures

The search was performed by the first author, after which all articles were imported to EndNote version 7.8 and duplicates removed. All article titles and abstracts were screened by two reviewers. A third reviewer was available to resolve any disagreements. A manual search of the reference lists of relevant studies was undertaken to identify any potentially relevant articles that were missed by the database search but that might be suitable for inclusion in the review. A full-text review of all suitable articles was undertaken and any study that did not meet the inclusion criteria was excluded, with the reasons for exclusion recorded in Appendix 5**.**

2.3.5 Data extraction

A standardized Microsoft Excel spreadsheet was created for data extraction. We attempted to contact the corresponding authors of included studies to obtain missing data and complete the data extraction form. The form included information on acceptance, completion, and dropout rates, as well as patient characteristics, a description of the intervention and comparison groups and data on the outcomes of included studies. Data from the first evaluation and those from any subsequent follow-ups were extracted. The quality of studies was defined based on the Cochrane risk-of-bias assessment tool(Higgins, Altman et al. 2011) Two independent reviewers performed the quality assessment for the included studies. Any disagreement between the reviewers regarding study eligibility and quality assessment was resolved by discussion. A third reviewer was available to resolve any persisting disagreements.

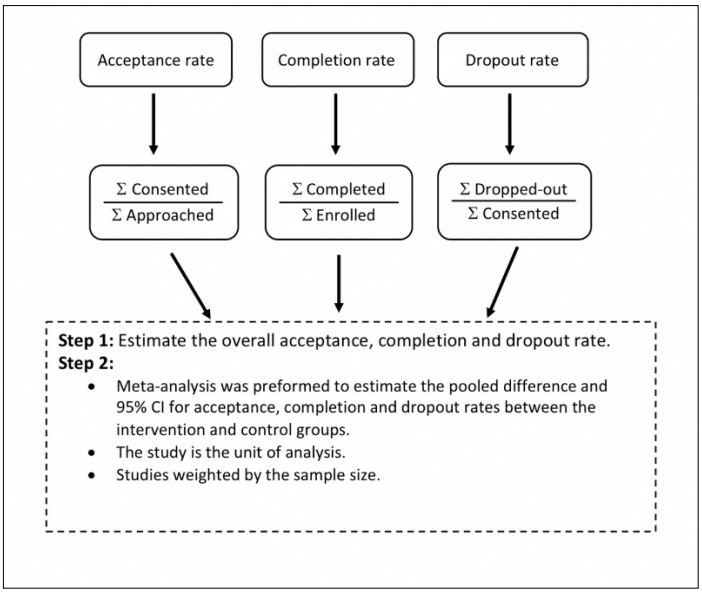
2.3.6 Data analysis

The results synthesis focused on key outcomes of interest including HRQoL and symptoms of COPD, acute exacerbations of the disease, lung function parameters, exercise capacity, and

antibiotic use, as well as acceptance, completion, and dropout rates. A meta-analysis was performed to estimate the pooled differences and 95% confidence intervals (CIs) in key outcomes between the OPEP group and the control group. The endpoint data after treatment exposure were used for analysis (Elbourne, Altman et al. 2002, Higgins and Green 2011). A random-effects model was used to obtain a conservative estimate. Continuous data are expressed as the mean difference (Δ). Standardized mean difference (SMD) was used when the same outcome was assessed with different measures. Dichotomous data are expressed as odds ratios (OR). Heterogeneity among included studies was assessed using the I-square (I^2) value. Publication bias was assessed with funnel plots for included studies. The statistical analyses were performed using the Cochrane Collaboration's Review Manager Software (RevMan version 5.2.0).

The overall acceptance rate was defined as the total number of participants who consented to participate divided by the number of participants who were approached for participation in the trial. The completion rate was defined as the total number of participants who completed the trial divided by the number of participants who enrolled in the trial and the dropout rate as the total number of participants in each treatment arm who dropped out from the study divided by the number of participants who consented to participate in the study(Alghamdi, Alhasani et al. 2018). Additional meta-analysis was preformed to estimate the pooled difference and 95% CI in acceptance, completion, and dropout rates between the OPEP and control groups. The estimation of rates weighted by the sample size in each study and data were pooled using random-effects models. All rates are expressed as proportions with 95% CIs. More information about the data analysis is provided in (Figure 2.1).

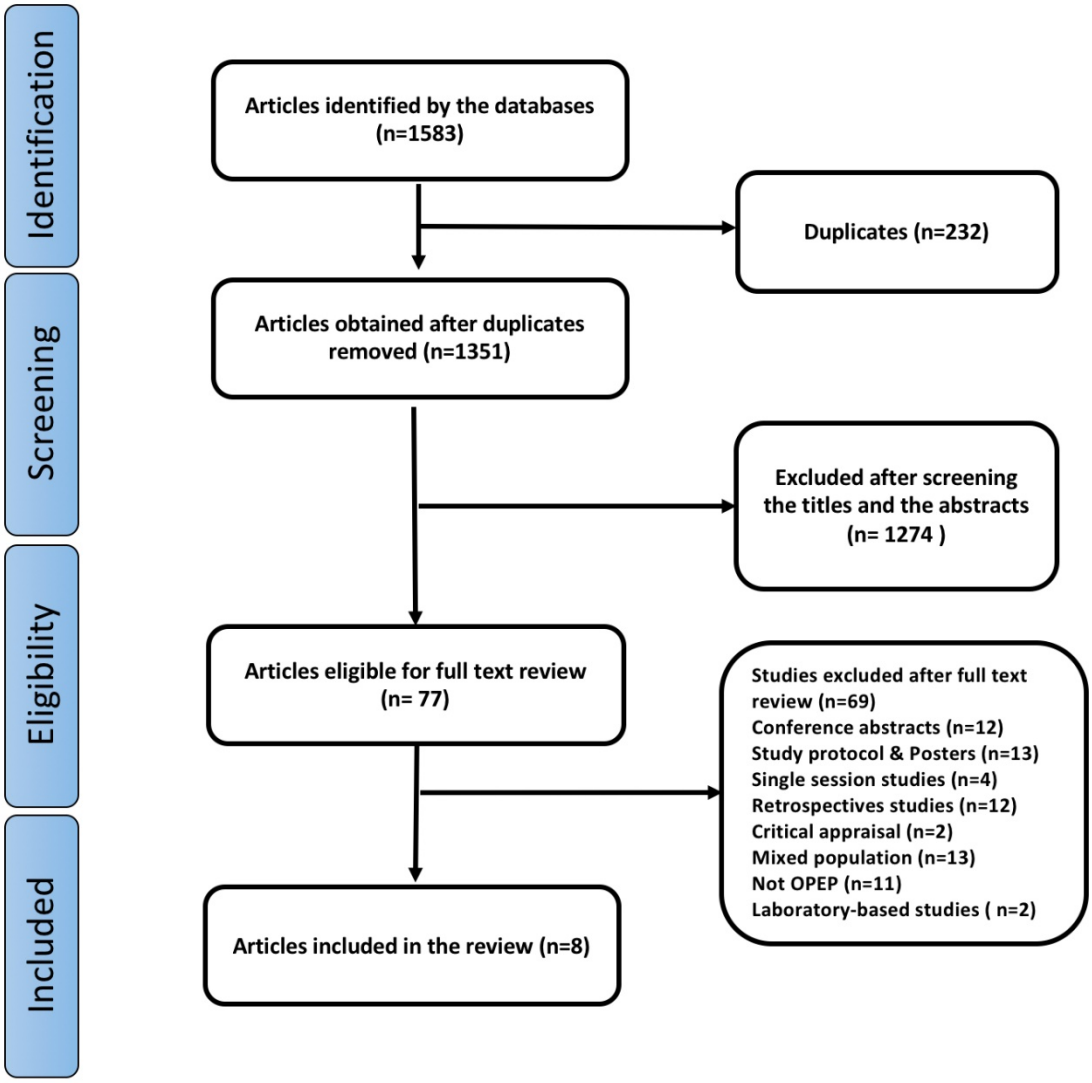
Figure 2.1 Statistical methods for acceptance, completion, and dropout rates.



2.4 Results

The search identified 1583 articles, 1351 after duplicates had been excluded, with a total of 77 articles retained for full-text review following title and abstract screening. After full-text review, eight articles were eventually considered for the review as outlined in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 2.2).

Figure 2.2 PRISMA Flow diagram showing studies related to the Oscillatory Positive Expiratory Pressure (OPEP) devices in COPD.



Six of the eight reports were randomised controlled parallel-group trials and two were crossover studies; the studies were published between 1996 and 2018. The eight included studies comprised a total of 381 patients with COPD, with sample sizes ranging from 15 to 120. Participant age (mean ± standard deviation) was 65 $\pm$ 7.4 years, and 61% were male. In total, 336

patients were recruited into trials of stable COPD, 45 during an acute exacerbation (AECOPD)(Weiner, Zamir et al. 1996, Cegla, Jost et al. 2002, Wolkove, Baltzan et al. 2004, Aggarwal, Shaphe et al. 2010, Sethi, Yin et al. 2015, Svenningsen, Paulin et al. 2016, Nicolini, Mascardi et al. 2018). Five studies were categorised as short term (<12 weeks), and three were categorised as long term, with duration up to 2 years. A range of comparisons were used including usual care (e.g. COPD medication regimen), ACBT, Pulmonary Rehabilitation (PR), and sham devices (Weiner, Zamir et al. 1996, Cegla, Jost et al. 2002, Wolkove, Baltzan et al. 2004, Aggarwal, Shaphe et al. 2010, Sethi, Yin et al. 2015, Svenningsen, Paulin et al. 2016, Nicolini, Mascardi et al. 2018). A summary of included studies is provided below in Table 2.1**.**

In the included studies, a range of different OPEP devices were used (e.g., Acapella [Smiths-Medical, Dublin, OH, USA], Flutter [Allergan, Inc., Dublin, Ireland], Aerobika [Monaghan Medical Corporation, Plattsburgh, NY, USA], Lung Flute [Medical Acoustics, Buffalo, NY, USA], and RC-Cornet [Cegla Medical Technology, Montabaur, Germany]). Funnel plot analysis revealed a symmetrical distribution, suggesting an absence of publication bias (Figure 2.3).

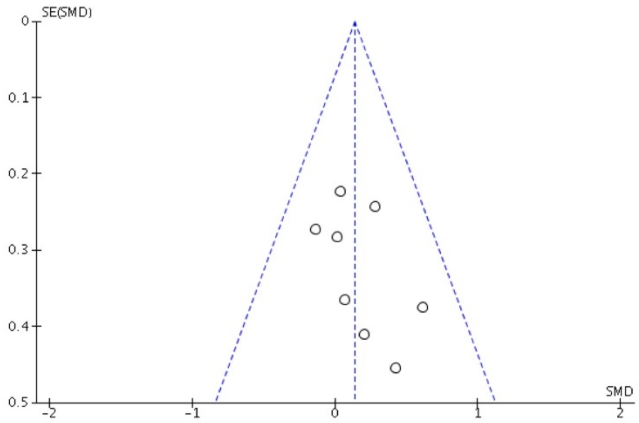
Table 2.1 Summary of included studies.

(Author, Year)	Patient group design	OPEP device	Treatment duration	Follow up	Control	Results of OPEP group compared to corresponding groups
(Aggarwal, Shaphe et al. 2010)	Hospitalised AECOPD RCT	Flutter n=15	15-mins, 3x per day, for 5 days	Every day	**Control 1:** ACBT n=15 **Control 2:** pursed lip breathing n=15	Flutter and ACBT had the same effect on lung function compared to pursed lip breathing (ΔPEFR; +30 L/min) Flutter reduced hospital stay compared to ACBT and pursed lip breathing (3/5/5 days)
(Cegla, Jost et al. 2002)	Stable COPD FEV_1 40±14% RCT	RC-Cornet plus UC n=25	>5-mins, 3x per day, for 2 years	Every 3 months	UC n=25	RC-Cornet had the same effect as UC on lung function (ΔFVC%; predicted +2%) RC-Cornet reduced antibiotic use compared to UC (12/25 vs 24/25) RC-Cornet reduced exacerbations over 2 years compared to UC (5/25 vs 12/25) RC-Cornet had the same effect as UC on hospital stays (17 vs 18 days).
(McCarroll 2005)	Stable COPD with hypersecretion RCT	Acapella plus PR n=12	10 - mins, 2x per week, for 8 weeks	Every 4 weeks	**Control 1:** UC n=11 **Control 2:** PR n=12 (2 sessions per week, for 8 weeks)	Acapella had the same effect as UC & PR on lung function (Δ FEV_1 and PEFR; +0.28 L/min and +16 L/min) Improvement in exercise capacity did not differ significantly between UC and PR (Δ6MWD; +44 m vs +54 m)
(Nicolini, Mascardi et al. 2018)	Stable COPD FEV_1=31±10% RCT	Lung Flute plus UC n=40	30-mins, 2x per day, for 12 days and then 26 weeks follow up	Every 4 weeks	**Control 1:** Flutter n=40 (30-mins, 2x per day, for 12 days and then 26 weeks follow up) **Control 2:** UC n=40	Lung Flute and Flutter reduced exacerbations compared to UC (7/40 vs 9/40 vs 11/40) Lung Flute and Flutter improved exercise capacity vs UC (Δ6MWD; +18.4 m/+11.5 m / -4.8 m) Lung Flute, Flutter, and UC;no difference in cough or sputum clearance (Δ BCSS score; -3/ -3.1/-3.5) Lung Flute and Flutter improved HRQoL compared to UC (Δ CAT score; -7.5/-6.4/-1.6) Lung Flute and Flutter reduced dyspnoea compared to UC (ΔMMRC score; -0.6/-0.4/+0.1)
(Sethi, Yin et al. 2015)	Stable COPD with sputum production, FEV_1 50±3% RCT	Lung Flute plus UC n=33	5-mins, 2x per day for 26 weeks	Every 8 weeks	UC n=36	Lung Flute reduced symptoms compared to UC (Δ CCQ score; -0.23 vs +0.01) Lung Flute improved HRQoL compared to UC (ΔSGRQ score; -3.23 vs -1.85, p=0.03) Lung Flute reduced exacerbations compared to UC (6/33 vs 14/36, p=0.03)

						Lung Flute improved exercise capacity compared to UC (∆6MWD; +7 m vs -42 m)
(Svenningsen, Paulin et al. 2016)	Stable COPD- sputum producer vs non-sputum producer FEV_1 60±18% RXT	Aerobika plus UC n=27	20-mins, 4x per day, for 3 weeks (one-week intervention, one-week washout, and one-week UC)	Not reported	UC	Aerobika improved lung function compared to UC (∆ FVC% predicted; +6%, p=0.005) Aerobika improved HRQoL compared to UC (∆SGRQ score; -9, p=0.01). Aerobika improved sputum clearance compared to UC (∆PEQ- ease-bringing-up-sputum; -1.2, p = 0.005) Aerobika improved exercise capacity compared to UC (∆ 6MWD; +19 m, p = 0.04) Aerobika improved regional ventilation compared to UC (∆ 3He MRI ventilation deficit percent; -1%).
(Weiner, Zamir et al. 1996)	Stable COPD FEV_1 35±8.5% predicted RCT	Flutter n=10	10 mins, 4-8x per day for 3 months.	Not reported	Sham Flutter 10 mins, 4-8 times/day for 3 months. n=10	Flutter and Sham Flutter no effect on lung function (∆FVC% predicted +2% vs +2%) Flutter improved exercise capacity vs Sham Flutter (∆12-minute walk distance; +649 m vs +538 m)
(Wolkove, Baltzan et al. 2004)	Stable COPD with sputum production and smoking history FEV_1 50±15% RXT	Flutter plus UC n=15	10-mins, 4x per day, for 1 week	Every week	Sham Flutter 10-mins, 4x per day, for 1 week	Flutter improved lung function vs Sham Flutter (∆ FVC%; +24%, p=0.05) Flutter improved exercise capacity vs Sham Flutter (∆ 6MWD; +10 m, p=0.05) Flutter reduced dyspnoea vs Sham Flutter (∆ Borg scale; +1, p=0.05)

Abbreviations: **∆:** Data presented as mean difference in absolute values between groups; **x:** Sessions per day**; RXT:** Randomised crossover trial**; RCT**: Randomised control trial; **N:** Number of participants**; OPEP**: Oscillatory Positive Expiratory Pressure; **ACBT:** Active Cycle of Breathing; **PR**: Pulmonary Rehabilitation; **I**: Intervention; **UC:** Usual Care; **C**: Control; **FVC**: Force Vital Capacity; **FEV1**: Forced Expiratory Volume in 1 second; **FEV1/FVC %:** FEV1/FVC ratio percentage; **PEFR:** Peak Expiratory Flow Rate; **SGRQ**: St. George's Respiratory Questionnaire; **CCQ**: Clinical COPD Questionnaire; **FVC%:**predicted forced vital capacity; **MMRC**: Modified Medical Research Council; **6MWD:** Six-minutes Walking Distance; **MRI:** Magnetic Reasoning Imaging ; **BCSS**: The breathlessness, cough and sputum scale; **3He:** Hyperpolarized 3 Helium

Figure 2.3 Funnel plot for detection of publication bias



2.4.1 Use during AECOPD

Only one study evaluated the impact of OPEP (Flutter) during hospitalisation for AECOPD(Aggarwal, Shaphe et al. 2010). Aggarwal et al. performed an RCT of 45 patients with AECOPD, and found that use of the Flutter device, ACBT and pursed lip breathing were associated with no difference in peak expiratory flow rate (mean difference [95% CI], 6.91 L/min [-52.1 L/min to 65.9 L/min]). However, patients who used the Flutter spent less time than the usual care group (3 vs 5 days)(Aggarwal, Shaphe et al. 2010).

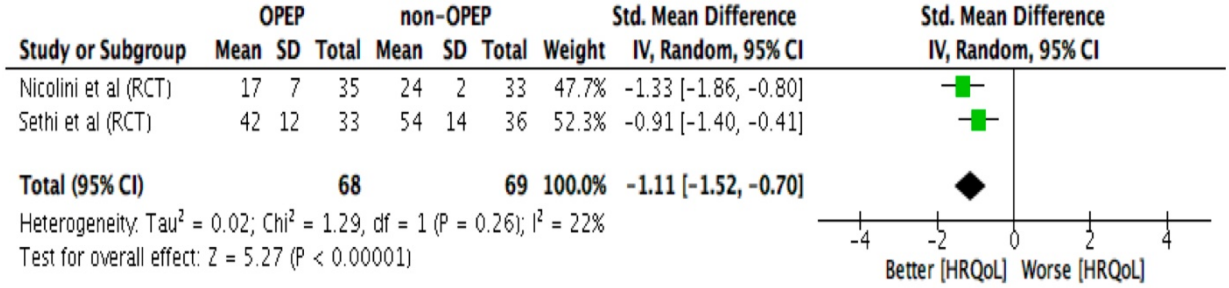
2.4.2 Stable COPD

2.4.2.1 HRQoL, symptoms and AECOPD

The impact of OPEP devices on HRQoL and symptoms of COPD was assessed in three studies using disease-specific questionnaires (e.g. SGRQ [St. George's Respiratory Questionnaire] and CAT [COPD Assessment Test])(Sethi, Yin et al. 2015, Svenningsen, Paulin et al. 2016, Nicolini, Mascardi et al. 2018). The meta-analysis for HRQoL is shown in Figure 2.4. Pooled analysis from two RCTs (n=137)(Sethi, Yin et al. 2015, Nicolini, Mascardi et al. 2018) showed that the

use of an OPEP device (Lung Flute) improved HRQoL compared to routine care (SMD [95%], -1.11 [-1.52 to -0.70], p<0.001). Similarly, 3 weeks use of the Aerobika was associated with improvement in HRQoL assessed using the SGRQ compared to UC (mean ± standard deviation; Aerobika 38±12, UC 49±14; p=0.01). It was not possible to assess the effect of OPEP device on the separate SGRQ domains, which included activity, symptoms and influence because of incomplete data(Svenningsen, Paulin et al. 2016).

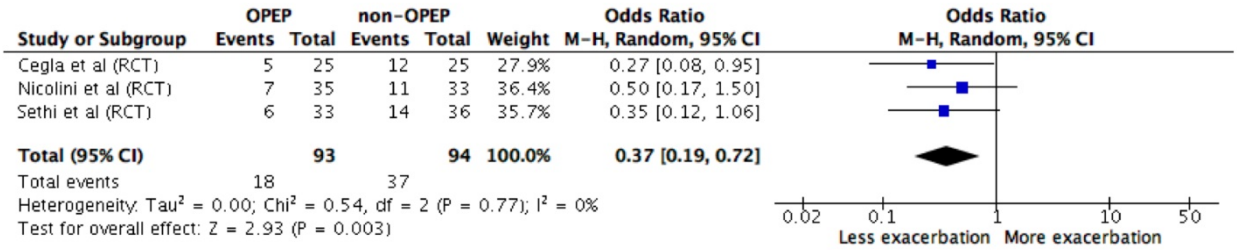
Figure 2.4 Forest plot comparing HRQoL measures (CAT and SGRQ) scores in OPEP interventions vs non-OPEP interventions.



2.4.2.2 Number of exacerbations

Figure 2.5 presents the study outcomes for number of exacerbation events (Sethi, Yin et al. 2015, Nicolini, Mascardi et al. 2018). In the pooled analysis of three RCTs (n= 187) reporting data on exacerbation events during follow-up, the Lung Flute and RC-Cornet were effective for reducing exacerbations events after 6-months compared to routine care (OR [95% CI], 0.37 [0.19 to 0.72]; p = 0.003) (Sethi, Yin et al. 2015, Nicolini, Mascardi et al. 2018).

Figure 2.5 Forest plot comparing exacerbation events six-months following the OPEP use (Lung Flute) vs usual care in stable COPD.



2.4.2.3 Antibiotic use

Antibiotic use was measured in one long term study, which found that use of the RC-Cornet (twice a day) for 2 years reduced the number of patients who took a course of antibiotics but that reduction was not statistically significant(13/25 vs. 24/25; OR [95% CI], 0.54 [0.22 to 1.29]; p=0.16)(Cegla, Jost et al. 2002).

2.4.2.4 Sputum clearance

Only one study measured the sputum clearance outcome (Svenningsen, Paulin et al. 2016). A 3-week RXT found that use of the Aerobika device improved sputum clearance (assessed with the Patient Evaluation Questionnaire (PEQ)-ease-bringing-up-sputum) in COPD patients with sputum production compared to UC (mean difference ± standard deviation; Aerobika 2.70±1.10, UC 3.60 ±0.50; P=0.003)(Svenningsen, Paulin et al. 2016). In this context, a reduced PEQ score indicates improved sputum clearance(Svenningsen, Paulin et al. 2016).

2.4.2.5 Lung function

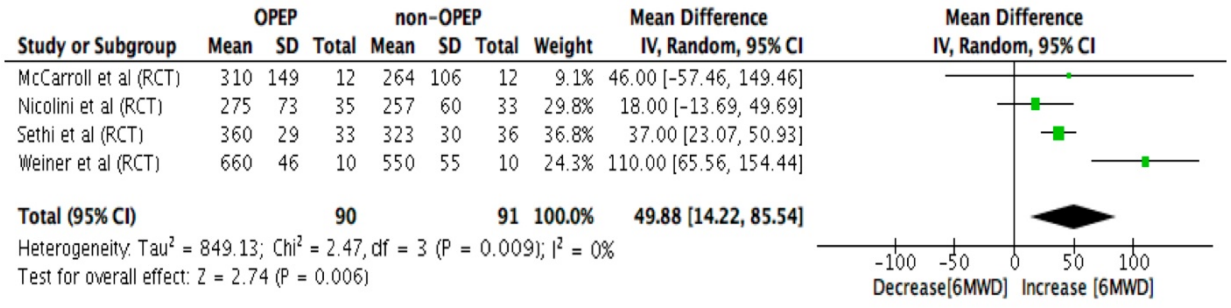
The impact of OPEP devices on measures of lung function was measured in six studies using a range of devices (RC-Cornet, Acapella, Flutter, and Aerobika). The studies used a range of parameters including forced expiratory volume in 1 second (FEV_1), peak expiratory flow rate (PEFR), and predicted forced vital capacity (FVC%), and overall, the use of OPEP devices had

no effect on lung function(Weiner, Zamir et al. 1996, Cegla, Jost et al. 2002, Wolkove, Baltzan et al. 2004, McCarroll 2005, Aggarwal, Shaphe et al. 2010, Svenningsen, Paulin et al. 2016).

2.4.2.6 Exercise capacity

Exercise capacity, assessed using six-minute walk distance (6MWD), was reported in six studies (Figure 2.6) (Weiner, Zamir et al. 1996, Wolkove, Baltzan et al. 2004, McCarroll 2005, Sethi, Yin et al. 2015, Svenningsen, Paulin et al. 2016, Nicolini, Mascardi et al. 2018). Pooled analysis of four RCTs (n=181) demonstrated an improvement following use of OPEP (e.g., Acapella, Lung Flute, and Flutter) compared to the control group, with the mean effect exceeding the minimal clinical important difference (MCID) for the 6MWD(Holland, Spruit et al. 2014) (mean difference [95%CI], 49.8m [14.2m to 85.5m]; p=0.009)(Weiner, Zamir et al. 1996, McCarroll 2005, Sethi, Yin et al. 2015, Nicolini, Mascardi et al. 2018). In contrast, data from two RXTs using OPEP (e.g., Aerobika and Flutter) did not demonstrate a significant improvement compared to usual care (Wolkove, Baltzan et al. 2004, Svenningsen, Paulin et al. 2016).

Figure 2.6 Forest plot comparing exercise capacity measured with 6MWD (in meters) in OPEP interventions vs non-OPEP interventions (RCTs data only).



2.4.2.7 Acceptance, completion, and dropout rates

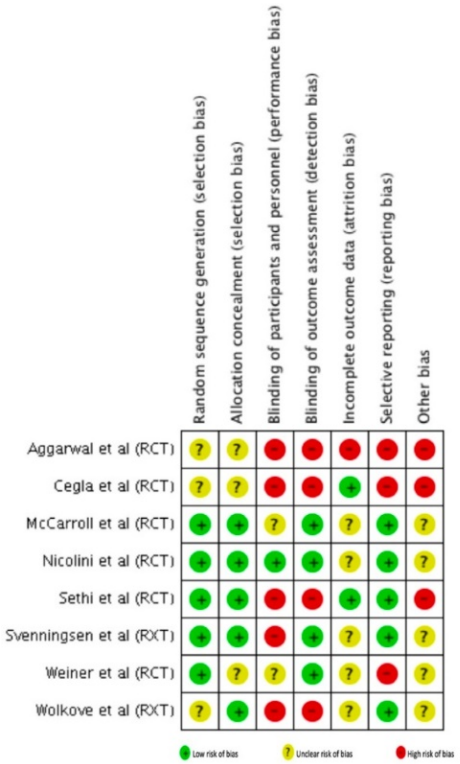
The total number of patients with COPD approached to take part in the included studies was 463. Of these, 82 patients were deemed ineligible and were excluded. 339 participants were enrolled in the studies with intervention and control groups, of whom 177 were assigned to the intervention group, and 162 to the control group. Forty-two participants were enrolled in the crossover studies.

After randomisation, 350 participants completed their interventions, and 31 withdrew before the end of the study. Of these, the reasons for study withdrawal were 'lost to follow-up' (66%), exacerbations (16%), death (6%), back pain (6%), discomfort during MRI (3%), and unknown (3%). Overall, the unweighted average of acceptance, completion and dropout rates for all included studies were 82%, 91% and 6%, respectively. Additionally, we performed a meta-analysis to estimate the pooled difference in acceptance, completion, and dropout rates between the OPEP groups and the control group for all included studies (weighted by the sample size). The pooled analysis demonstrated significant differences in acceptance and completion, but not in the dropout rate between the OPEP and control groups (mean difference [95%CI], 63% [58% to 67%]; p<0.001, 58% [53% to 63%]; p<0.001, and 3% [1% to 6%]; p=0.21) respectively.

2.4.3 Risk of bias assessment

Using the Cochrane risk-of-bias assessment tool,(Higgins, Altman et al. 2011) the studies included showed considerable variation in the risk of bias, but most were limited by a lack of blinding and incomplete reporting of data. A summary of our judgments on the potential risk of bias is provided in Figure 2.7.

Figure 2.7 Assessment of risk of bias for included studies.



2.5 Discussion

In the context of COPD, improving sputum clearance and sputum production are desirable objectives, both in terms of day to day symptoms and HRQoL, and for reducing the risk of acute exacerbations. These findings suggest that the use of OPEP devices has the potential to reduce COPD symptoms and exacerbations, reduce antibiotic use, and improve exercise capacity in people with COPD. Nevertheless, questions remain regarding the use of OPEP devices, including their general effectiveness, the relative effectiveness of different types of device, the best strategy for their use (regular, or as required), the threshold of symptoms at which adjunct devices should be recommended (as benefits are likely to be largest in those for whom sputum production is a major concern), longer term impacts and acceptability, as well as their value relative to other interventions. Some evidence supports the use of an OPEP device to reduce exacerbations. However, the effects observed were generally modest,

results were based on a limited number of trials with considerable variation in the risk of bias, and most trials were short-term.

Although sputum production is an important symptom for patients, this is a relatively neglected area in COPD. The Global Initiative on Obstructive Lung Disease 2019 (Vogelmeier, Criner et al. 2019) and joint American Thoracic Society/European Respiratory Society COPD guidelines(Qaseem, Wilt et al. 2011) do not make any reference to sputum clearance techniques (searched using the words 'sputum', 'clearance' and 'physiotherapy'), although NICE COPD guidance for stable COPD (1.2.99) recommends that "If people have excessive sputum, they should be taught: how to use positive expiratory pressure devices and the active cycle of breathing techniques"(Hopkinson, Molyneux et al. 2019). The term "excessive" is not defined here and it is not clear if the use of OPEP might also benefit people with persistent but less severe symptoms of sputum production, not meeting this notional threshold.

In COPD, sputum clearance might be expected to reduce airflow obstruction and allow occluded lung units to be recruited (Mohamed, Badr et al. 2019). Included studies have shown contrasting results; however, one study reported a reasonable response in lung function parameters such as FEV_1 and PEFR immediately after an OPEP session(Wolkove, Kamel et al. 2002). Nonetheless, lung function parameters appear to be relatively insensitive to regular use of OPEP devices.

Meta-analysis of RCTs demonstrated improvements in 6MWD exceeding the MCID(Holland, Spruit et al. 2014) with longer term OPEP device use(Weiner, Zamir et al. 1996, McCarroll 2005, Sethi, Yin et al. 2015, Nicolini, Mascardi et al. 2018), though results from cross-over studies were less compelling (Wolkove, Baltzan et al. 2004, Svenningsen, Paulin et al. 2016). As expected, patients with sputum production were more likely to improve than those

without, (Salh, Bilton et al. 1989, Svenningsen, Paulin et al. 2016) suggesting that patient stratification is needed to identify a responder phenotype, as with other interventions.

The included studies used a variety of devices; all demonstrated a reasonable acceptance and completion rate and OPEP device intervention trials seem generally acceptable among people with COPD. Regrettably, data comparing the effectiveness of OPEP devices are limited. Here, the largest improvements in COPD symptoms, exacerbation and HRQoL were seen with the use of the Acapella, Lung Flute and Aerobika devices. By contrast, fewer improvements were recorded for the Flutter. This may simply reflect study population recruited or other aspects of study design, but it could be due to device features such as the pattern of pressure waves the OPEP devices can produce or the usability of the device itself(Mueller, Bersch-Porada et al. 2014). Direct comparison studies are needed to establish whether factors such as the consistency of pressure amplitude and frequency or the level of resistance are important. Some devices, such as Acapella and Aerobika, have a valve for adjustable resistance while other OPEP devices do not. Taken together, these differences and similarities are factors which may influence device efficacy and optimal mechanical performance both between devices generally and in terms of variations between individual patient response or preference(Suggett, Meyer et al. 2014, Van Fleet, Dunn et al. 2017, Thanh, Jacobs et al. 2019).

In the included studies, COPD was described as either acute or stable. These brief descriptions of the disease are inadequate for determining the clinical phenotype in such a heterogeneous condition. Of the included studies, only one stratified participants into sputum producers or non-producers. Accordingly, we recommend that future studies stratify the COPD profile according to the amount of sputum produced as a step towards developing personalised approaches to COPD care (Agusti, Bel et al. 2016, Bourbeau, McIvor et al. 2019). In the

included studies, most dropouts were for patient-related reasons; specifically, patients mostly discontinued OPEP trials because of exacerbations. Thus, attention must be paid to accommodate these when designing OPEP trials of COPD. Other factors should also be considered, such as the cognitive ability required to perform OPEP exercise adequately and the need for support and training to maintain correct use.

A number of lessons can be learned from this analysis. First, most of the clinical trials had varied data measurement and collection for specific outcomes such as cough, sputum production, dyspnoea and HRQoL. Second, most of the clinical trials failed to blind the patients and participants, as well as outcome assessors. Third, addressing missing data was not clearly discussed in the published studies. This is important because it introduces the risk of bias in trial outcomes, and consequently weakens the evidence regarding the effectiveness of OPEP devices for COPD. Unfortunately, the available clinical trials still do not provide sufficient information regarding the OPEP long-term effectiveness and value with COPD. An additional contribution of this review is to inform future clinical study design regarding the acceptance, completion and dropout rates of OPEP device trials in COPD. Moreover, this review will also help researchers understand the reasons that prevent patients with COPD from completing OPEP therapy and provides evidence for the short-term use of OPEP in COPD management. Finally, outcomes of this review have informed the design of the randomised clinical trial reported in chapter 4.

2.6 Limitations

There are several limitations that should be considered when interpreting the results of this review and should be addressed in future research. First, this meta-analysis excluded single-session studies and included only studies that evaluate the short-and-long impact of OPEP

devices on key outcomes (e.g., HRQoL, exacerbations, and exercise capacity). However, the exclusion of single-session studies is not expected to have had an effect on the overall results of this review, as it is hard to evaluate the acute impact of a single-session of OPEP device on a prolonged outcome such as HRQoL. In addition, the meta-analysis included different study designs (e.g. RCTs and RXTs) with different quality levels. Furthermore, there were limited opportunities to pool results for key outcomes because of incomplete data. Future research needs to evaluate the impact of OPEP devices within different types of study designs (e.g. pre/post studies) as well as report the outcomes of interest using gold-standard measures.

2.7 Conclusion

The use of OPEP devices may have a positive impact on patients with COPD. However, well-designed clinical trials are needed to examine the long-term impact of OPEP devices in well-defined specific patient cohorts. Data should be collected using valid measures and questionnaires to allow for comparison between studies and direct comparisons between devices are needed.

3 Methods and Materials

The methods described here are related to the O-COPD clinical trial described in chapters 4,5, and 6.

3.1 Study design

An assessor-blind randomised single-blind controlled parallel group for three months comparing provision of Oscillatory Positive Expiratory Pressure (OPEP) device and usual care in patients with COPD. A subset of 45 participants underwent measurement of objective cough monitoring and sleep actigraphy.

3.2 Study setting

Participants in the O-COPD trial (described in chapters 4,5, &6) were recruited from the Royal Brompton Hospital in London, UK. I obtained an honorary contract as a clinical research fellow and respiratory physiotherapist to gain access to facility and patient data.

3.3 Ethical consideration

The O-COPD clinical trial (described in chapters 4,5&6) were given the essential ethical approval to be conducted in the UK by the Health Research Authority (HRA), Health and Care Research Wales (HCRW), and London-Chelsea Research Ethics Committee (REC). The ethical committee at Royal Brompton and Harefield NHS foundation Trust committee approved the O-COPD and the cough clinical studies on 28/11/2019 and the ethics number is 19/LO/1427. The ethical approval letter is shown in Appendix 1. The Written consents were obtained for all participants. All the studies were conducted based on the Good Clinical Practice (GCP) guidelines. Trial registration: ISRCTN44651852 https://www.isrctn.com/ISRCTN44651852

3.4 Potential participants

Recruitment for the studies in chapters 4,5&6 was carried out between February 2020 to October 2021 at the Royal Brompton Hospital. All studies recruited COPD patients only with written informed consent to participate in the studies. Potential participants were identified in three ways:

(i) When participants come into contact with the primary care teams, secondary care clinics, community clinics, or 6 months after pulmonary rehabilitation reviews.

(ii) An existing list of potential research participants including those willing to participate in clinical research or those who have completed pulmonary rehabilitation programs.

(iii) By advertisement (local boards and newspapers and through the British lung foundation network of Breath easy groups.

3.4.1 Participant's eligibility

Participants were stable COPD patients with reporting a productive cough (daily or most days in the preceding month). To quantify that at screening, participants were asked to complete a self-reported sputum frequency scale (Appendix 2). The sputum frequency scale had one question: *How often do you cough up sputum?* The possible answers were *Every day*, *Several days a week*, *Almost every day in the last month*, *On a few days in the last month*, and *Only with lung or respiratory infections*. Participants were classified-based on their answers. One of the first three answers were required for the eligibility criteria.

3.4.1.1 Inclusion criteria

- Adults with clinical diagnosed COPD confirmed by spirometry (defined as forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio <70%, and have frequently produce sputum: every day or most days in the last month.
- Achieve a total score of ≥5 out of 10 in cough and phlegm items (Items 1&2) on the COPD Assessment Tool (CAT) score (Appendix 3).
- Stable COPD with no exacerbations or change in medication regimen on the last four weeks.

3.4.1.2 Exclusion criteria

- Unable to provide informed consent.
- A major condition limiting life expectancy to three months.
- Referral for chest physiotherapy in the preceding year.
- Already on OPEP devices for sputum clearance during the baseline measurement, although people who have used OPEP devices in the past were not excluded.
- Within one month of pulmonary exacerbations, COPD medication change, or pneumothorax.

3.5 Sample size

The primary endpoint was between group change in cough-related quality of life, measured using the Leicester cough questionnaire (LCQ). Based on a mean(SD) LCQ score of 14.5(2.3) in stable COPD(Berkhof, Doornewaard-ten Hertog et al. 2013) to detect the proposed minimum clinical important difference (MCID) (Ramos, Krahnke et al. 2014, Rebelo, Oliveira et al. 2020) , a change

of 1.3 points between study groups, with 80% power at a significance level of 0.05 would require 102 participants, yielding a recruitment target of 120 allowing for 15% dropout rate.

3.6 Screening

Potential participants were screened initially by telephone call due to the COVID-19 pandemic. All medical history, demographic data, health status, exacerbation events, medications lists, pulmonary and blood test results data were collected using a standardised case report form (CRF) and transferred to a standardised spreadsheet after obtaining written consent form.

3.7 Randomisation, allocation, and blinding

In the O-COPD trial and cough study (chapters 4 and 6), consented participants were randomised using an online system from **www.SealedEnvelope.com** at the individual level with a 1:1 allocation and variable block size randomisation. The randomisation was to receive either an intervention or usual care. To ensure matching, randomisation, participants were stratified according to (1) exacerbation rate – whether patients have had <2 or ≥2 exacerbation events in the preceding year (2) Health status - COPD Assessment Test (CAT) score <20 or ≥20. Because of the nature of the intervention, par–icipants could not be blinded to treatment allocation, however the assessor at the follow-up was blinded and patients were asked not to reveal which study arm they had been in.

3.7.1 Usual Care

All participants were instructed about the ACBT (described in chapter 1) to enhance sputum clearance and advised to perform this three times per day. To ensure clinical care was standardised (Hopkinson, Molyneux et al. 2019) participants received British Lung

Foundation(BLF) and Association of Chartered Physiotherapists in Respiratory Care(ACPRC) leaflets on correct inhaler use, smoking cessation, and ACBT, as well as a link to online instructional videos.

3.7.2 Intervention

Participants who allocated to intervention arm received OPEP device (Acapella, Smiths Medical, Ohio, USA) additional to the usual care. Participants were taught how to use Acapella and received written information and a link to an appropriate online video. Participant advised to perform acapella three times per day.

3.7.2.1 Why I chose the Acapella

We chose Acapella as it is relatively low cost (£30 per device) and easy to use, and less time consuming (Belli, Prince et al. 2021). There are some manufacturing advantages in using acapella in airway clearance. First, acapella devices have an adjusted resistance valve (dial) that allows users to increase the oscillations (resistance). Second, the mean pressure generated by the acapella has higher and constant oscillations compared to other OPEP devices (Volsko, DiFiore et al. 2003). The Acapella is portable, easy to clean, and gravity independent, which means participants can use them anywhere and in any position. All these observations are supported by the clinical data that has demonstrated that the acapella device has been prescribed most in the COPD and non-COPD populations (Naraparaju, Vaishali et al. 2010, Tse, Wada et al. 2020). Furthermore, our group previously reported that there is a higher rate of preference for the acapella device compared to other OPEP devices among physiotherapy in the UK (Barker, Laverty et al. 2017).

3.7.3 Training on treatments

All participants allocated to treatments were instructed by a respiratory care therapist (Saeed) to do either OPEP or ACBT techniques three times a day for three months. Also, all the participants were directed to written materials and an online video link on how to perform OPEP or ACBT techniques at home. All participants were instructed that they can request a video conferencing call if needed (This has been added due to restrictions imposed during COVID-19 outbreak). A standardised phone call at six weeks was made to remind the participants and encourage compliance to use the treatments.

3.8 Assessment tools for cough outcome

A range of assessment tools for cough parameters are currently in use in clinical practice. These assessment tools are either subjective or objective measures or a mixture of both. Mostly, they evaluate the parameters of the cough, such as the severity, frequency, and cough related quality of life. This evaluation can be done from both the patient and the clinician perspective (Leconte, Ferrant et al. 2011, Cho, Birring et al. 2019). In this thesis, I have used the following cough assessment tools.

3.8.1 Subjective cough measurements

This form of measurement usually uses a self-administered questionnaire to obtain a numerical score that represents the severity of the cough or to what extent the cough impacts the overall health status and quality of life. Questionnaires such as the Leicester cough questionnaire (LCQ) and cough visual analogue scale (VAS) , are widely used in clinical practice (Cho, Birring et al. 2019).

3.8.1.1 Leicester cough questionnaire (LCQ)

Birring and his colleagues developed LCQ, which is a well-constructed cough-related quality of life questionnaire (Birring, Prudon et al. 2003). LCQ has 19 items covering three domains, which are physical, social, and psychological issues with cough. The responders use a 7-point Likert scale. The total score of LCQ is 21. A higher score indicates a better cough-related quality of life; a lower score indicates poor cough-related quality of life (Birring, Prudon et al. 2003, French, Fletcher et al. 2004). LCQ is widely used in COPD clinical research, particularly with chronic bronchitis patients. LCQ is a valid and reliable measure for use with COPD patients and it has a high internal consistency score between items (Cronbach alpha = 0.92); the repeatability score over two weeks is ICC = 0.96 (French, Fletcher et al. 2004). It has been identified as a responsive tool for successful treatment of patients with COPD. The MCID for LCQ is COPD patients is 1.3 point change (Birring, Prudon et al. 2003, Berkhof, Hertog et al. 2013).

3.8.1.2 Cough visual analogue scale (VAS)

The cough -VAS is widely used in clinical practice and research (Boulet, Coeytaux et al. 2015). VAS mostly measures cough severity. It consists of a scale in millimetres (mm) ranging from 0 to 100 mm (Birring and Spinou 2015). A higher score represents a worse cough, and a lower score represents a less severe cough. It is easy and only has one question to complete (Birring and Spinou 2015). Despite its wide use, VAS has not been extensively studied for validity and reliability (Birring and Spinou 2015, Boulet, Coeytaux et al. 2015). Researchers have been able to report a MCID of 17 mm with acute cough, but not with chronic cough patients, such as those with COPD (Lee, Matos et al. 2013).

3.8.2 Objective cough measurements

Objective assessment techniques for cough are a new and growing research field (Cho, Birring et al. 2019). These objectives measurements were developed to supplement subjective measurements and help in understanding the underlying mechanism of the cough rather than to treat the cough (Cho, Birring et al. 2019). For a better outcome, a cough assessment usually correlates both subjective and objective measurements, but objective measures have rarely used in clinical research (Smith, Owen et al. 2006, Kelsall, Houghton et al. 2011). Available objective measures can give outcomes concerning cough count, coughs per hour, and cough pattern (Cho, Birring et al. 2019). The objective cough monitor obtained in this thesis is the Leicester Cough Monitor (LCM) (Birring, Fleming et al. 2008).

3.8.2.1 Leicester cough monitor (LCM)

The Leicester cough monitor (Figure 3.1) is a semi-automated system to record and report cough frequency, developed by Birring and his colleagues (Birring, Fleming et al. 2008). The LCM consists of a small digital recorder with lapel microphone (Birring, Fleming et al. 2008). The monitor records the cough for more than 24 hours depending on the battery life as well as the monitor internal memory (Matos, Birring et al. 2007). A digital recording analysis by predetermined algorithm/custom software identifies the cough like sounds and the cough waves. The automated process of detecting the cough takes on average 40 minutes per 24 hours of cough recording; more recording time will need more processing time (Matos, Birring et al. 2007, Birring, Fleming et al. 2008). The cough count is then displayed in audio and visual form for refining by the human operator (5-15 minutes). The monitor provides a detailed report about the cough patterns in different forms, such as cough events, cough waves, and cough during day or

night (Matos, Birring et al. 2006). The monitor has been evaluated in several clinical studies, which show that the monitor is valid for detecting cough pattern in different populations with chronic cough, including COPD patients (Birring, Fleming et al. 2008). The LCM has high sensitivity and specificity, scoring 91% and 99%, respectively (Birring, Fleming et al. 2008), and the automated cough counts via LCM were found to be repeatable with ICC = 0.90. The LCM has been used in clinical research and is considered the simplest and easiest way to measure cough in COPD populations (Crooks, Hayman et al. 2016, Crooks, Den Brinker et al. 2017).

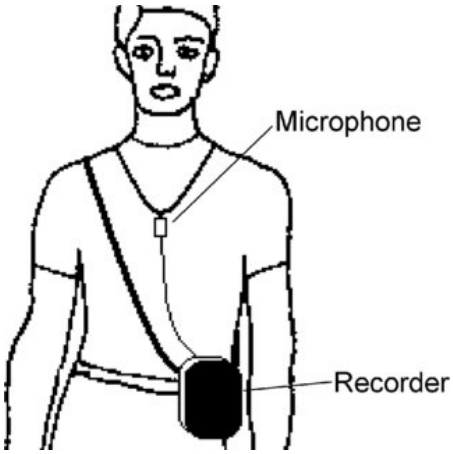


Figure 3.1 Leicester cough monitor.

3.8.2.2 Cough frequency recording process

The LCM consists of a portable mp3 voice tracer/player (LFH662, Philips, Netherlands) and Me-15 Tie clip microphone (Olympus, Tokyo, Japan). It uses a sound recording system combined with a software algorithm to detect cough frequency over 24 hours (24h). The LCM microphone is attached as close as possible to the larynx. During the recording, participants were instructed to wear the LCM, except when bathing, and continue their usual activities. A help desk and telephone line at the recruitment centre were in operation for 9 hours daily (8:00 am to 5:00pm) for troubleshooting and assistance. Written instructions and a patient diary also were given with

the monitor. The setup for the LCM was done at the clinic and the participants are instructed to wear the microphone once they receive the monitor. A follow up phone call is scheduled to operate LCM remotely over the phone. The participants are asked to keep the monitor on all the time. Sufficient battery was supplied with each monitor to make sure the participant did not run out of batteries. Participants are asked to return the monitor after completing 24 hours of recording. Paid special delivery envelopes were given to the participants.

3.8.2.3 Cough frequency analysis

The data obtained from the LCM were downloaded and analysed by myself using LCM software at King's College Hospital. As noted above, initial detection of the cough like sound was done by the LCM software, and the confirmation carried out by the investigator listening to the cough sound. The analysis of each 24 hrs of recording took an average ~ 40 minutes. 24h-cough frequency defined as the number of coughs during the 24 hours recording time. Nighttime cough was defined as cough events during sleeping hours. Cough frequency was expressed as number of coughs per 24 hours (24h cough frequency) and/or cough per hour.

3.9 Assessment tool for body movements during sleep

3.9.1 Measuring body movement

Despite the important benefits of the physical activity in COPD progression and management, it is also a complex factor to monitor and measure. The definition of physical activity includes any bodily movement produced by the contractions of skeletal muscle that increases energy expenditure above the basal level (Caspersen, Powell et al. 1985). Body movement during the day includes specific physical exercise or fitness activity, but also it includes the movements during sleep such as body postures and transitions due to cough or dyspnoea, which are known

as movement during sleep (Hartman, Prinzen et al. 2015). Body movement during sleep can reflect poor sleep quality in COPD (Agusti, Hedner et al. 2011, Hartman, Prinzen et al. 2015). It can be frequent and disturbing for COPD, and consequently cause fatigue(Agusti, Hedner et al. 2011). Movement during sleep can be measured objectively by sleep actigraphy. Movement during sleep is defined as the body movement after the patient went to the bed. Participants were asked to write down the time they went to bed and the time they wake up.

3.9.2 Sleep actigraphy

Sleep actigraphy is an accurate and reliable tool to track the nighttime body movements (Morgenthaler, Alessi et al. 2007, Spina, Casale et al. 2015, Spina, Spruit et al. 2017), which is increasingly used in clinical practice. The research in developing objective activity monitors is growing and there are a variety of sleep actigraph systems currently used in the clinical and research practice to track the routine body movement (Morgenthaler, Alessi et al. 2007). Actigraphy provides more precise information about the behaviour and the routine of the body movement during sleep(Bossenbroek, Gordijn et al. 2010); data thus obtained can be used to evaluate the association between physical activity and the clinical outcome (Spina, Spruit et al. 2017).

The monitor used in this thesis is the DynaPort MoveMonitor (McRoberts, The Hague, Netherlands). It is a triaxial accelerometers with multiple sensors to monitor different dimensions of the body movements. The DynaPort monitor is small monitor about the size of a credit card that the patient wears across their lower back. It is simple and reliable measure for body movement during sleep (Bossenbroek, Gordijn et al. 2010, Van Remoortel, Raste et al. 2012, Gloeckl, Damisch et al. 2015). In my thesis, it was chosen to capture the sleep disturbance related

to cough events. Further details about paired data from objective cough monitoring and sleep actigraphy described in chapter 5.

3.9.3 Sleep actigraphy monitoring process

The monitor was prepared at the clinic. Participants were instructed to wear the DynaPort, except when bathing, for 24 hours and continue their usual activities (Figure 3.2). The DynaPort was worn on a belt around the waist, with the device situated in the middle of the lower back. A help desk and telephone line at the recruitment centre were on operation for 9 hours daily (8:am to 5:00pm) for troubleshooting and assistance. Written instructions and patient diary also were given with the monitor. When the monitors were returned, data were downloaded to DynaPort software. The software processing data and provide a sleep movement report Table 3.1.

Table 3.1 DynaPort MoveMonitor parameters.

Parameter	Definitions
Nighttime activity	A description of the activity during the nighttime. (Night rest duration, lying down, getting out of bed and time spent out of bed)
Body postures	A description of the positions of the body against the time. It is always expressed as the position per mins (Right, left, supine, and prone).
Transitions	A description of the level and intensity of shifting from one position to another positions (Small, medium, large, extra-large, and sitting)

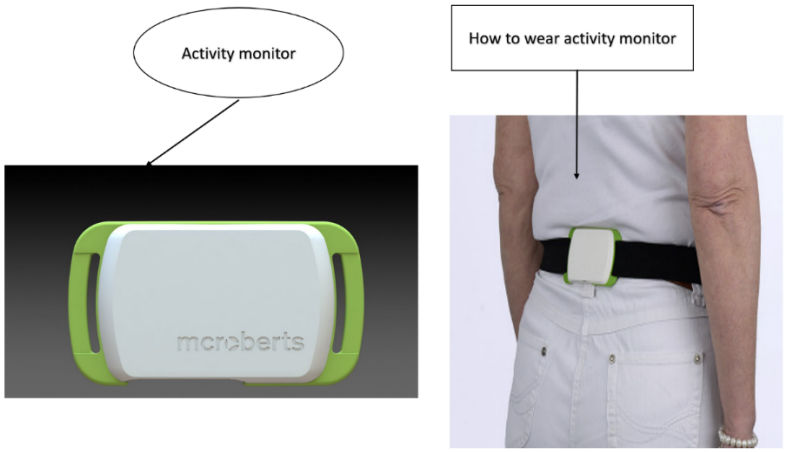


Figure 3.2 DynaPort MoveMonitor.

3.10 Other clinical outcomes

3.10.1 Pulmonary Function Testing

Recent spirometry results within the last 6 months were considered at the screening. If updated pulmonary function tests (PFT) were needed, it was carried out by one of the respiratory physiologists at the lung function unit at the Royal Brompton Hospital following the American Thoracic Society and European Respiratory Society guidelines for PFT testing (Brusasco, Crapo et al. 2005).

3.10.2 The COPD assessment tool (CAT)

The CAT score is a valid and quick questionnaire to evaluate eight domains in the COPD symptoms (cough, sputum, chest tightness, breathlessness, going up hills, activity limitations at home, confidence going out home, sleep and energy). Each domain has a range score from (0 = I'm very happy) to (5 = I'm very sad), and a total score 40. The higher the score the worst the symptoms and health status (Jones, Harding et al. 2009). Measuring the CAT score is a quick and simple way to assess symptoms in routine clinical practice, and CAT score was validated in more than 90 languages around the world (Jones, Harding et al. 2009). The CAT score is an effective way to

measure the changes in health status and clinical outcomes with COPD (Dodd, Hogg et al. 2011, Kelly, Bamsey et al. 2012). The Intraclass Correlation Coefficient (ICC) for the reliability of the CAT score has ranged from 0.85 to 0.98, and the MICD has been reported as a 2 unit change in the total score (Gupta, Pinto et al. 2014, Kon, Canavan et al. 2014).

3.10.3 Self-identified sputum frequency scale

The self-identified sputum scale is a quick and simple questionnaire, that categorises sputum productions into 5 categories. These descriptions are “Every day”, “Several days a week”, “Almost every day in the last month”, “On a few days in the last month”, “Only with lung or respiratory infections.” The first three descriptions consider the participants as regular sputum producers, and the last two consider the patient as non-regular sputum producers. The questionnaire used first in clinical research by Svenningsen et al 2016 (Svenningsen, Paulin et al. 2016, Svenningsen, Guo et al. 2017). It is a practical and simple way to describe the frequency of sputum production with COPD (Svenningsen, Guo et al. 2017).

3.10.4 Functional Assessment of the chronic illness therapy-fatigue scale (FACIT)

The Functional Assessment of the Chronic Illness Therapy-Fatigue Scale (FACIT) is a 13-item scale to examine fatigue in COPD. Each item has an option from “not at all” to “very much”, that option is a score from 0-4. Total score of fatigue is calculating by adding up all item’s scores. The total score for FACIT is 52, the higher score represents more energy and less fatigue (Al-Shair, Muellerova et al. 2012). FACIT is a valid and reliable tool to assess fatigue in COPD. The reliability has been reported between ICC= 0.92 and 0.93 (Al-Shair, Muellerova et al. 2012). Published MCIDs of FACIT range from 2.8 to 6.8)(Nordin, Taft et al. 2016).

3.10.5 EuroQol-5 Dimensions (EQ-5D)

EQ-5D is a simple and valid questionnaire to measure the general health related quality of life in chronically ill patients including COPD. EQ-5D has a visual scale in the number range from 0 to 100 mm to score the general health. Zero represent the worst imaginable health, and 100 represent the best imaginable health (Pickard, Wilke et al. 2008). EQ-5D has been found valid, reliable, and responsive to measure the impact of COPD in health (Hoyle, Tabberer et al. 2016, Nolan, Longworth et al. 2016, Bae, Choi et al. 2020, Guo, Chen et al. 2020).

3.10.6 Exacerbation history

An exacerbation of COPD (AECOPD) refers to an acute deterioration in the COPD symptoms. AECOPD usually requires medical interventions such as administration of antibiotics and/or steroids and may result in hospital admission. AECOPD are often reported by the patients in routine clinical practice, but some may go underreported or are self-medicated by patients with prior agreement with their physician. Measuring AECOPD in clinical practice is still controversial. Alternative ways to report AECOPD events are either patient's diaries and/or patient-reported outcomes (Aaron 2014). A small, but significant body of literature, has reported healthcare innovations such as telemonitoring and Artificial Intelligence (AI) to predict the exacerbations before it happens, the results are promising, and it could replace the traditional methods of reporting AECOPD outcomes (Fernandez-Granero, Sanchez-Morillo et al. 2018, Alghamdi, Aldhahir et al. 2020, Alghamdi, Rajah et al. 2021). In my thesis, information about AECOPD was collected at baseline and at 6 weeks phone call. The patients were asked how many AECOPD episodes had they experienced in the past year, and we did the same at the 6 weeks phone call. AECOPD is defined as an episode that requires antibiotics +/- oral steroids.

3.10.7 Patient diary card

A standardised diary card given to participants to document and track any changes in the COPD symptoms, hospital admissions, change in medications, use of the interventions or usual care, hours spend out the home.

3.11 Statistical analysis

Between-group differences were compared using linear mixed models adjusted for baseline values as a covariate. Data analysis was on an intention to treat basis, and complete case analysis is also presented as a sensitivity analysis. Correlation between variables assessed by Pearson correlation of Spearman rho as appropriate. Data analysis was performed using SPSS version 26.0 (IBM, SPSS, Illinois, USA) and Prism 9.2 (GraphPad Software Inc, California, USA). The distribution of the data was checked by Shapiro-Wilk and Kolmogorov-Smirnov tests. The baseline characteristics were expressed as mean and standard deviation, median and interquartile ranges, frequencies and proportions, as appropriate. The logarithmic transformation was used for skewed data to normalise the distribution and expressed as geometric means (GEM) and logarithmic standard deviation (LogSD). Transformation applied only for cough data (Sumner, Woodcock et al. 2013).

3.11.1 Handling missing data

Missing data from questionnaire outcomes were imputed based on last observation carried forward (LOCF)(Rezvan, Lee et al. 2015). Considering the validity of imputation involves two steps: 1) comparing the baseline differences on the outcome within the treatment group, such

as those with missing data to those without missing data in the intervention group; and 2) comparing the baseline differences on the outcome between groups, such as those with missing data and those without missing data. When there are no differences, imputation is used.

3.11.2 Additional analysis

Any additional statistical analysis was described related to each chapter

4 Oscillatory Positive Expiratory Pressure (OPEP) Therapy in Chronic Obstructive Pulmonary Disease (COPD): The O-COPD Randomised Clinical Trial

4.1 Abstract

Rationale: Oscillatory Positive Expiratory Pressure (OPEP) devices can be used by people with COPD to facilitate sputum clearance, but there is limited evidence for their effectiveness, or to guide patient selection. We therefore conducted an assessor-blind, parallel group randomised controlled trial to evaluate whether adding an OPEP device (Acapella) to usual care (including the use of the active cycle of breathing techniques (ACBTs)) for three months would improve cough-related quality of life measured with the Leicester Cough Questionnaire (LCQ) in COPD patients who reported that they had produced sputum every day or most days in the last month.

Methods: The O-COPD study (ISRCTN Registry: 44651852) recruited participants between February 2020 and October 2021. Eligible COPD patients (defined as forced expiratory volume in 1 s (FEV_1)/ forced vital capacity (FVC) ratio <70%) needed a score of ≥5 out of 10 in the first two items (cough and sputum) of the CAT score, with no exacerbations or change in medications in the previous month. Patients were randomly allocated 1:1 to either intervention (the Acapella choice, Smiths Medical) or to usual care. All participants received training and were advised to perform sputum clearance at least three times per day. The primary endpoint was between-group change in LCQ after three months. Secondary endpoints included changes in general quality of life, fatigue score and sputum frequency scale. Change was compared between groups using the linear mixed models, adjusting for

baseline values using SPSS version 26. Data are presented as percentage (%) or (mean±SD) or mean difference (MD) and 95% confidence intervals [CI].

Results: 122 participants were recruited (OPEP n=61, UC n=61) and 103 completed the study (OPEP n=55, UC n=48). Participants were aged 62±10 years, 40% were female, 17% were smokers, and FEV_1 (L) 1.08 (0.78 to 1.60). Change in LCQ favoured the OPEP group (MD and [95% CI]; +1.03 [0.71 to 2.18]; p= 0.03). There were also statistically significant differences between groups in the fatigue score (+4.68 [1.34 to 8.02]; p< 0.001, EQ5D quality of life (+.004 [0.49 to 19.75]; p= 0.04 and sputum frequency scale +0.44 [0.27 to 0.60]; p<0.001), favouring the OPEP treatment.

Conclusion: Adding the OPEP device to usual care for three months improves cough-related quality of life and was accompanied by improvement in fatigue, general quality of life, and sputum expectoration. These findings support the use of OPEP device in COPD patients with regular sputum production.

Trial Registration: ISRCTN44651852

4.2 Introduction

A frequent productive cough is associated with a poorer quality of life in people with COPD (Hartman, Prinzen et al. 2015). The failure to clear airway secretions contributes to lung damage and increases the local inflammatory burden. This increases the risk of respiratory exacerbations and their consequences beyond the lungs (Ramos, Krahnke et al. 2014). In addition, AECOPDs are a leading cause of hospital admissions. Interventions to reduce their occurrence would be of great public health value. Earlier in this thesis we learned that people with COPD often experience a productive cough due to mucus hypersecretion. Having an effective cough that clears mucus can be challenging due to hyperinflation, respiratory muscle dysfunction, and premature airway collapse (van der Schans, Postma et al. 1999, Hopkinson, Sharshar et al. 2004, Hopkinson, Dayer et al. 2010, Omachi, Blanc et al. 2012, Zwerink, Brusse-Keizer et al. 2014, Baz, Haji et al. 2015). Thus, COPD patients with coexisting bronchitis are at greater risk of having these problems that results in poor airway clearance mechanism (Martinez-Garcia and Miravitlles 2017).

Improving airway clearance is, therefore, a potentially important goal in treating COPD(Bourbeau, McIvor et al. 2019). In chapter 3 of this thesis, I reviewed the evidence that demonstrated that the addition of OPEP devices to usual care could contribute to reducing hospital length of stay, reducing exacerbations, improving short-term health status, and exercise tolerance. These conclusions are still uncertain as they are based on a limited number of trials with a small number of participants (Barker, Laverty et al. 2017, Alghamdi, Barker et al. 2020), but suggest a randomised controlled trial would be worthwhile.

Related to this project, our group previously analysed English prescribing data from the primary care to explore the actual use of OPEP devices and the attitude of physiotherapists

toward these devices (Barker, Laverty et al. 2017). The clinical data showed that OPEP usage was lower than medications, but physiotherapists believe that OPEP devices are effective in treating COPD (Barker, Laverty et al. 2017).

In the NICE guidelines (1.2.40 and 1.2.99), symptomatic sputum production in COPD is currently recommended to be treated with oral therapy or ACBTs, but not with OPEP devices (Hopkinson, Molyneux et al. 2019). Although some studies suggest a positive impact from the short-term use of OPEP devices in people with COPD (Alghamdi, Barker et al. 2020, Daynes, Jones et al. 2021), little is known about the long-term impact or patient selection. In other words, no clinical consensus exists regarding OPEP recommendations within COPD management plans. The rationale for this could be the evidence deficits in providing clear recommendations for OPEP devices use, particularly with COPD patients for whom sputum production is a concern. Coughing (with or without sputum) occurs both during the day and at night. During the night, coughing may be associated with in-bed movements, which may indicate a sleep disturbance or getting out of bed. COPD patients who frequently produce sputum have rarely been studied for this phenomenon, and clinical outcomes have mostly been reported as subjective assessments (Hartman, Prinzen et al. 2015). There is little research on the relationship between cough, sputum production, sleep disruption, and fatigue in COPD patients. Another gap in the evidence base is the absence of clinical trials that have evaluated the long-term impact of OPEP devices in COPD patients, and finally studies that have evaluated whether OPEP devices have an impact on quality of life. Oscillatory Positive Expiratory Pressure (OPEP) Therapy in Chronic Obstructive Pulmonary Diseases (the O-COPD trial), which will be reported in this chapter, addresses these gaps and objectives are as follows:

- In COPD with frequent sputum production, to what extent adding the OPEP device (Acapella) to the usual care for three months would improve the cough-related quality of life, compared to the usual care?
- In a subset group from the O-COPD trial, I will describe the cough frequency and its association with sleep movements, using objective monitoring systems. This will be discussed in chapter 5.

- In the same subset group, I will examine whether using the OPEP device for three months would lead to reductions in objective cough monitoring and sleep movements, compared to usual care. This will be discussed in chapter 6.

4.3 Methods

For details on methods, please refer to chapter 3.

4.4 Primary endpoint

The primary endpoint was the between group change in cough-related quality of life, measured with the LCQ at three months(Birring, Prudon et al. 2003). A higher LCQ score indicates a better cough-related quality of life.

4.5 Secondary endpoints

4.5.1 Fatigue score

Between group change in fatigue was measured using Functional Assessment of Chronic Illness Therapy (FACIT) (Al-Shair, Muellerova et al. 2012). A higher score indicates less fatigue.

4.5.2 Generic health-related quality of life

Between group change in generic health-related quality of life assessed with the EQ-5D questionnaire (Nolan, Longworth et al. 2016). A higher score of EQ-5D indicating a better quality of life.

4.5.3 Cough severity

Between group change in the cough severity was assessed using a cough-visual analogue scale (Cough-VAS) from 0 to 100mm (Kelsall, Decalmer et al. 2008). A higher score of Cough -VAS indicates a worse cough.

4.5.4 Sputum frequency scale

Between group change in sputum production was measured by the self-reported sputum scale used by Svenningsen et al. (Svenningsen, Paulin et al. 2016). The score for the sputum scale was from 1 to 5, with the higher score indicating that the patient was less bothered by sputum daily.

4.5.5 Number of exacerbations

We collected data about AECOPD at baseline and at the six-week phone call.

4.5.6 Health status and COPD symptoms

Between group change in health status was assessed with CAT Assessment Tool (Jones, Harding et al. 2009). A higher score of CAT indicates worse symptoms.

4.5.7 Sub study endpoints

In a subset group from the O-COPD trial, I was interested in recording cough frequency and sleep parameters using objective monitoring systems. All patients were invited to wear

additional objective cough monitoring devices and actigraphy to evaluate sleep movement. The data will be reported in subsequent chapters (5 and 6).

4.5.8 Study procedures

Full details about the study procedures, visits, and measurements for the O-COPD trial (Figure 4.1)

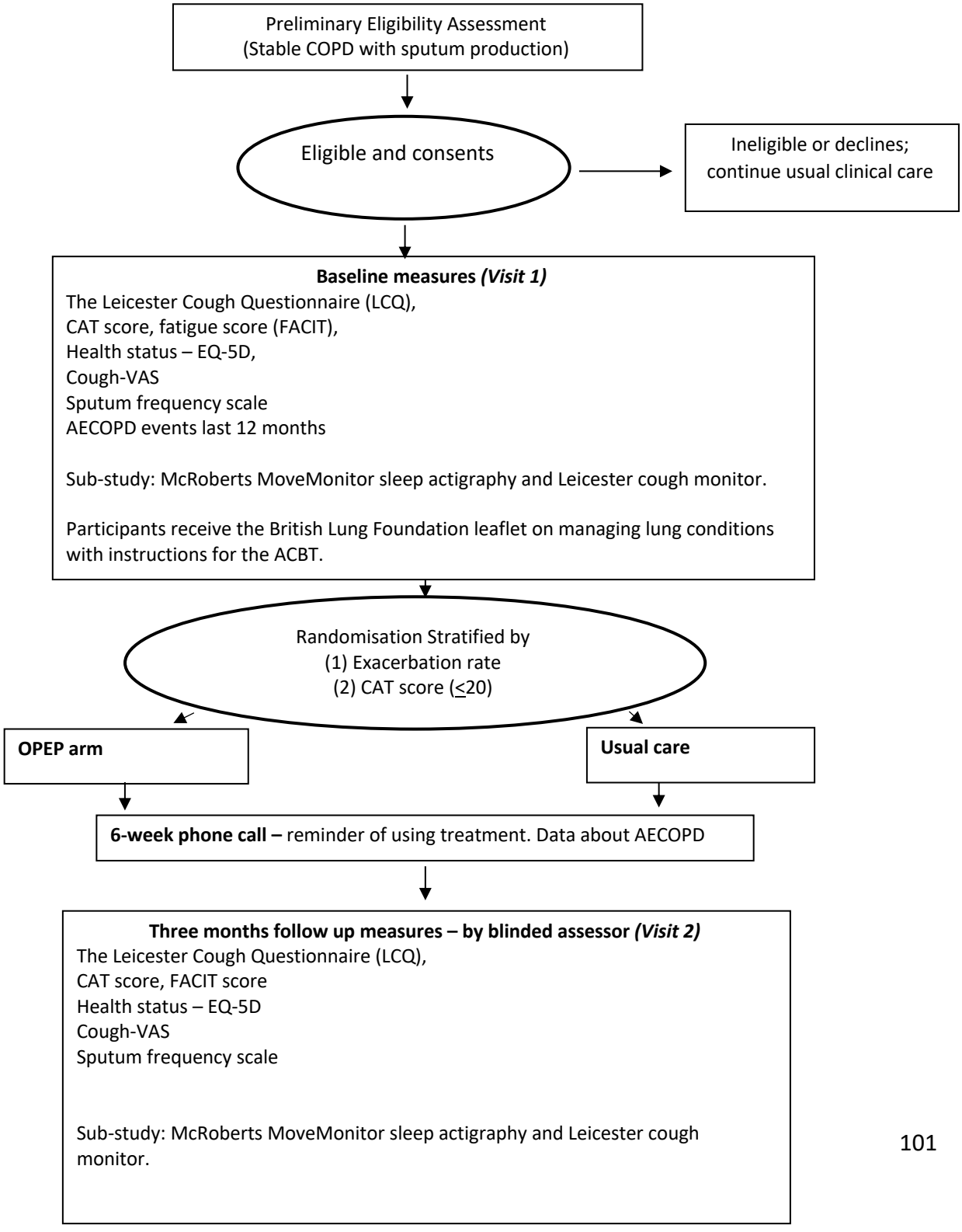


Figure 4.1 A flow diagram for the study procedures.

4.5.9 Statistical analysis

The baseline characteristics were expressed as mean and standard deviation (SD), median and interquartile ranges (IQR), and frequencies and proportions (%), as appropriate. The distribution of the data was checked using normality tests. Between-group (intervention and usual care) differences were compared with linear mixed models with adjustment to the baseline values. The between-groups difference was presented as mean difference (MD) and 95% confidence interval [CI] or chi-square. Pearson's correlation test was used to assess the relationship between the continuous variables. P-value <0.05 was considered statistically significant. Handling missing data from questionnaires was based on the last observation carried forward (LOCF) imputation method (Rezvan, Lee et al. 2015). Data analysis was on an intention to treat basis SPSS version 26 (IBM, SPSS, Illinois, USA) and Prism 9.2 (GraphPad Software Inc, California, USA). Results for study completers only, without imputed data are also presented for information. Additional analysis has been performed for the primary outcome (LCQ). The additional analysis summarise the data based on to the first two items from the CAT (cough and sputum).

4.6 Results

The participants were recruited between February 2020 and October 2021 at the Royal Brompton Hospital in London. Last patient last visit (LPLV) was on October 15, 2021. I approached and reviewed 379 potential participants, of whom 122 were allocated to either intervention (n=61) or usual care (n=61). Of these 103 completed the study (OPEP n=55 and usual care n=48). Six (9%) dropped out from the intervention group and 13 (21%) dropped

out from the usual care. In the OPEP arm, one patient joined another trial, two patients dropped out due to side effects, and three patients were lost to follow up. Full details about the included and excluded participants, as well as reasons for dropping out, are described in the CONSORT diagram (Figure 4.2). Table 4.1 shows the baseline characteristics for both the intervention and usual care groups.

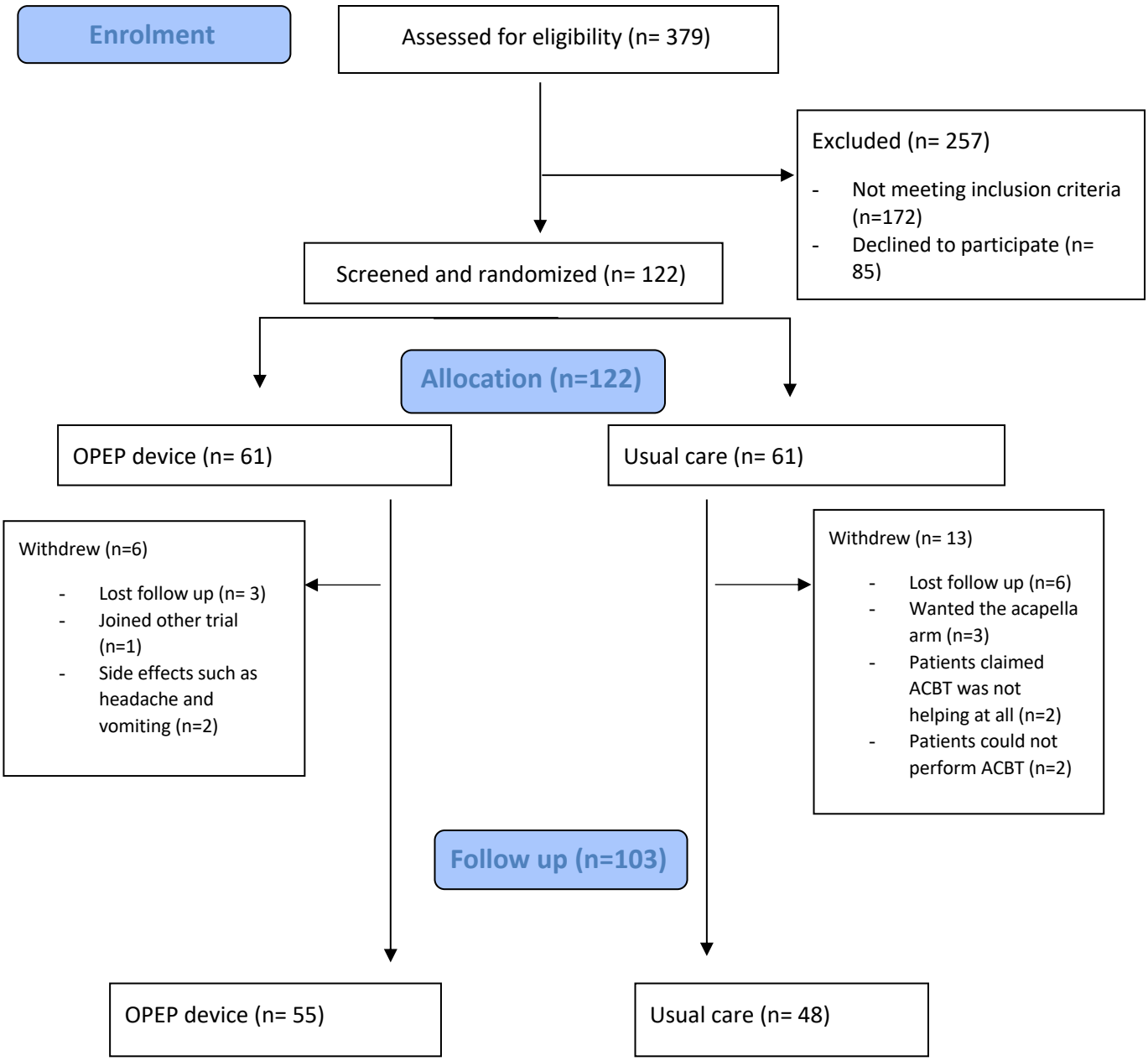


Figure 4.2 CONSORT flow diagram for the participants in the O-COPD trial.

Table 4.1 Baseline characteristics for all participants.

Characteristics	Sample (122)	OPEP (n=61)	Usual care (n=61)	p-value
Age	62.54±10.27	64.24±10.35	60.85±9.99	0.06
Gender (Female)	49(40.2%)	25(41%)	25(40%)	0.85
Ethnicity				
White British	98(80.3%)	46(75.4%)	52(85.2%)	0.10
Other	18(14.8%)	13(21%)	5(8.2%)	
Had tried an OPEP device previously (Yes)	15 (12.3%)	11(18%)	4(6.6%)	0.08
Watching instruction videos				
Once	69(56.6%)	30(49.2%)	39(63.3%)	0.27
Twice	38(31.1%)	23(37.7%)	15(24.6%)	
More than three times	14(11.5%)	7(11.5%)	7(11.5%)	
Pack years§	15[12-26]	15[11-20]	20[12-37]	0.10
Smoking history				
Smoker	21(17.2%)	11(18%)	10(16.4%)	0.81
Ex-smoker	101(82.8%)	50(825)	51(83.6%)	
Diagnosis				
COPD I	12(9.8%)	9(14.8%)	3(4.9%)	0.24
COPD II	29(23.8%)	13(21.3%)	16(26.2%)	
COPD III	50(41%)	26(42.6%)	24(39.3%)	
COPD IV	31(25.4%)	13(21.3%)	18(29.5%)	
AECOPD last year				
No	36(29.5%)	22(36.1%)	14(23%)	0.14
1	29(23.8%)	15(24.6%)	14(23%)	
2	15(12.3%)	10(16.4%)	5(8.2%)	
3	9(7.4%)	3(4.9%)	6(9.8%)	
>3	18(14.8%)	6(9.8%)	12(19.7%)	
Previous Pulmonary Rehabilitation (Yes)	70 (57.4%)	33(54.1%)	37(60.7%)	0.42
Medication lists				
Inhalers (yes)	113(92.6%)	53(86.9%)	60(98.4%)	0.05
ICSc (Yes)	82(67.2%)	37(60.7%)	45(73.8%)	0.12
Mucolytics (Yes)	59(48.4%)	32(52.5%)	27(44.3%)	0.36
Azithromycin (Yes)	22 (18.8%)	12 (21.8%)	10 (20.8%)	0.90
Lung Volumes				
FEV1 Litre§	1.08 [0.78-1.60]	1.12[0.80-1.74]	1 [0.69-1.47]	0.13
FEV1 % §	38[26-56]	43[26-63]	37[25-46]	0.09
FVC Litre §	3[2.34-3.67]	3[24-3.6]	3[2.22-3.69]	0.70
FVC % §	86 [70-98]	88[72-98]	84[65-98]	0.52
FEV1/FVC ratio % §	37 [28-46]	36[28-50]	37[28-45]	0.73
TLC%§	134 [120-146]	136[125-150]	134[114-142]	0.61
RV% §	211[156-253]	189[156-261]	223[156-253]	0.73
RV/TLC §	55[43-66]	51 [41-64]	60.50[47-67]	0.88
TLCO % §	35.5 [27-60]	31.50[21.3-66.50]	36.15[31-79]	0.63
KCO % §	44[28-53]	44[26-51]	39[21-66]	0.82

Abbreviations: SD, standard deviation; IQR, interquartile range; GOLD, Globel initiative for chronic obstructive lung disease; AECOPD, Acute exacerbation of COPD; FEV1, Forced expiratory volume in one second; FEV1%; predicted force expiratory volume in one second; FVC, forced vital capacity; FVC%, predicted forced vital capacity; TLC% , predicted total lung capacity; RV% , predicted residual volume; TLCO% , predicted diffusing capacity for carbon monoxide; KCO%, predicted carbon monoxide transfer coefficient; LCM, Leicester cough monitor. § the data reported as median and IQR.

4.6.1 Primary outcome

The between group difference in the total LCQ score at the end of the study was statistically significant after adjustment for the baseline values (MD and 95%CI; 1.03 [0.71 to 2.18], p =0.03). The size of the difference did not meet MCID of 1.3, although this difference did lie within the confidence intervals. Among LCQ domains, there was a statistically significant difference in the LCQ psychological domain between the intervention and the usual care group, favouring the intervention group (MD and 95% CI: 0.48 [0.22 to 0.90], p=0.02). There were no statistically significant differences between groups in the physical or social domains. Complete case analysis without imputation has demonstrated the same results (Figure 4.3, Table 4.2, and Table 4.3)

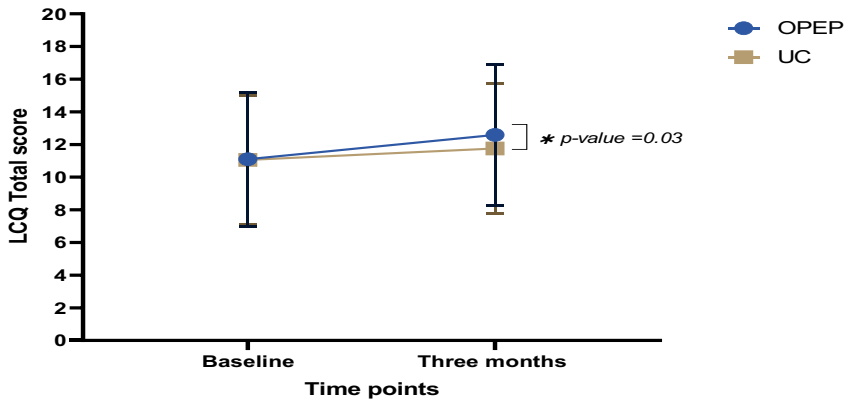


Figure 4.3 Between group change at baseline and after three months.

Table 4.2 Between group changes in LCQ and its components (intention to treat).

	OPEP (n=61)			UC (n=61)			Between groups	
	Pre	**Post**	**Change ± SD (95%CIs)**	**Pre**	**Post**	**Change ± SD (95%CIs)**	**MD [95% CI]**	**p-value**
Total LCQ	11.09±4.01	12.63±4.28	1.54±4.07(0.33,2.18)	11.06±3.93	11.67±3.97	0.51±2.81(0.34,1.89)	1.03 [0.71 to 2.18]	0.03
Physical	4.51±1.54	4.99±1.91	0.48±2.00(-0.40,0.75)	4.36±1.53	4.66±1.51	0.30±1.05(-0.20,0.77)	0.18 [-0.01 to 0.80]	0.06
Psychological	4.01±1.66	4.72±1.74	0.74±1.65(0.3,1.02)	4.26±1.61	4.49±1.64	0.23±1.17(-0.05, 0.75)	0.51 [0.06 to 0.90]	0.02
Social	2.55±1.16	2.85±1.09	0.29±0.82(-0.06,0.52)	2.43±0.97	2.49±0.98	0.06±0.82(-0.42,0.25)	0.23 [-0.08 to 0.44]	0.18

Note: Mean difference within groups = post– pre. **MD**= Between group differences compared with linear mixed model adjusted for the baseline values.

Table 4.3 Between group changes in LCQ and its components (complete case analysis).

	OPEP (n=55)			UC (n=48)			Between groups	
	Pre	**Post**	**Change**	**Pre**	**Post**	**Change**	**MD [95% CI]**	**p-value**
Total LCQ	10.95±4.03	12.55±4.29	1.60±4.34	10.55±3.94	11.64±3.95	1.09±2.69	0.51 [0.04 to 2.10]	0.04
Physical	4.44±1.54	4.96±2.34	0.51±2.14	4.16±1.54	4.65±1.53	0.49±0.98	0.03 [-0.63, 0.69]	0.07
Psychological	3.09±1.66	4.7±2.19	0.78±1.76	4.04±1.61	4.47±2.35	0.40±1.2	0.38 [0.04, 0.98]	0.03
Social	2.55±1.16	2.85±1.36	0.29±0.89	2.32±0.97	2.51±0.97	0.19±0.78	0.11 [-0.23, 0.42]	0.13

Note: Mean difference within groups = post– pre**. MD**= Between group differences compared with linear mixed model adjusted for the baseline value

4.6.2 Secondary outcomes

4.6.2.1 Fatigue score (FACIT)

The fatigue score was statistically significantly different between the intervention and usual care groups. MD [95%CI]: +4.68 [1.34 to 8.02]; p <0.001, favouring the OPEP treatment (More details about secondary outcomes are provided in Table 4.4 and Table 4.5).

4.6.2.2 Generic health related quality of life

There was statistically significant difference between groups in the EQ-5D questionnaire. MD [95%CI]: +4.00 [0.49 to 19.75]; p =0.04, favouring the OPEP treatment.

4.6.2.3 Cough-VAS

The between-group difference was not statistically significant in Cough-VAS.

4.6.2.4 CAT score

There was no statistically significant difference between groups in the CAT total score.

4.6.2.5 Sputum frequency scale

There was a statistically significant difference between the groups concerning the sputum frequency scale, with a notable reduction in the people who received OPEP treatment compared to usual care (MD [95%CI]; 0.44 [0.27 to 0.60]: p < 0.001).

4.6.2.6 Exacerbation events during the study

The number of AECOPD events at the six-week phone call was significantly lower in the OPEP treatment group compared to the usual care (Table 4.6). AECOPD events were reported in 44 out of 103 participants. Of those, 18 (32%) were in the Acapella arm, and 26 (54%) were on the usual care. The difference between groups in AECOPD was statistically significant (OR [95%CI], 0.41 [0.18 to 0.91]; p = 0.029).

Table 4.4 Between group changes in secondary endpoints (intention to treat).

	OPEP (n=61)			UC (n=61)			Between groups	
Outcome	**Pre**	**Post**	**Change**	**Pre**	**Post**	**Change**	**MD [95% CI]**	**p-value**
FACIT	27.16±12.65	32.98±12.82	5.82±13.32	27.03±12.25	28.17±13.06	1.14±13.01	4.68 [1.34 to 8.02]	<0.001
EQ5D	52.38±23.61	58.29±27.48	5.91±26.71	52.57±25.09	54.48±25.31	1.91±19.60	4 [0.49 to 19.75]	0.04
VAS cough	51.95±24.97	51.60±26.73	-0.32±19.88	54.18±25.56	51.95±26.98	-2.23±25.31	1.91 [-5.53 to 8.3]	0.68
CAT	31.32±9.03	29.36±10.36	-1.96±7.10	32.62±8.50	30.81±8.88	-1.81±5.83	0.15 [-1.93 to 1.63]	0.18
Sputum scale	1.33±0.65	1.84±0.88	0.50±0.97	1.41±0.79	1.47±0.77	0.06±0.92	0.44 [0.27 to 0.60]	<0.001

Note: Mean difference within groups = post– pre; FACIT: Functional Assessment of Chronic Illness Therapy. **MD**= Between groups difference compared with linear mixed model adjusted for the baseline values.
Positive change in FACIT, EQ5D, Sputum frequency scale denotes better outcome.
Negative change in Cough-VAS and CAT score denotes better outcome.

Table 4.5 Between groups changes in secondary endpoints (complete case analysis).

	OPEP (n=55)			UC (n=48)			Between groups	
Outcome	**Pre**	**Post**	**Change**	**Pre**	**post**	**Change**	**MD [95% CI]**	**p-value**
FACIT	26.25±12.31	33.22±12.74	6.97±13.68	26.70±12.11	27.90±13.09	1.20±13.43	5.77 [3.13 to 8.41]	0.03
EQ5D	51.28±22.69	58.79±27.41	7.51±27.10	50.81±24.48	52.65±25.56	1.84±24.26	5.67 [0.44 to 10.91]	0.04
VAS cough	51.83±25.26	50.24±26.83	-1.59±22.72	52.85±24.62	50.34±26.15	-2.51±25.13	0.92 [-3.47 to 5.31]	0.82
CAT	30.81±9.23	28.51±10.39	-2.30±8.13	33.58±8.18	31.50±8.85	-2.08±6.78	0.22 [-1.35 to 1.79]	0.48
Sputum scale	1.36±0.67	1.87±0.89	0.51±1.00	1.51±0.85	1.55±0.82	0.04±1.03	0.47 [0.27 to 0.66]	<0.001

Note: Mean difference within groups = post– pre; FACIT: Functional Assessment of Chronic Illness Therapy. **MD**= Between groups difference compared with linear mixed model adjusted for the baseline values.
Positive change in FACIT, EQ5D, Sputum frequency scale denotes better outcome.
Negative change in Cough-VAS and CAT score denotes better outcome.

Table 4.6 Between groups change in AECOPD.

	OPEP group (n=55)	UC (n=48)	Total	OR [95%]	p-value
AECOPD reported	18(32%)	26(54%)	44 (42%)	0.41 [0.18 to 0.91]	0.029
No AECOPD	37(68%)	22 (46%)	59 (58%)		

Note: AECOPD; Acute exacerbation chronic obstructive pulmonary diseases. AECOPD events count if the participant started rescue pack.

4.6.2.7 Association at baseline between LCQ and other measurements.

As shown in Table 4.7 and Figure 4.4, there was an association between LCQ and FACIT (r=0.60; p <0.001). Cough-VAS was moderately associated with the LCQ (r= -0.42; p<0.001). All the associations were statistically significant.

Table 4.7 Association at baseline LCQ and other measurements.

Questionnaires	Correlation coefficient (r)	p-value
FACIT	0.60	<0.001
EQ-5D	0.50	<0.001
Cough-VAS	-0.42	<0.001
CAT	-0.56	<0.001
Sputum frequency scale	0.44	<0.001

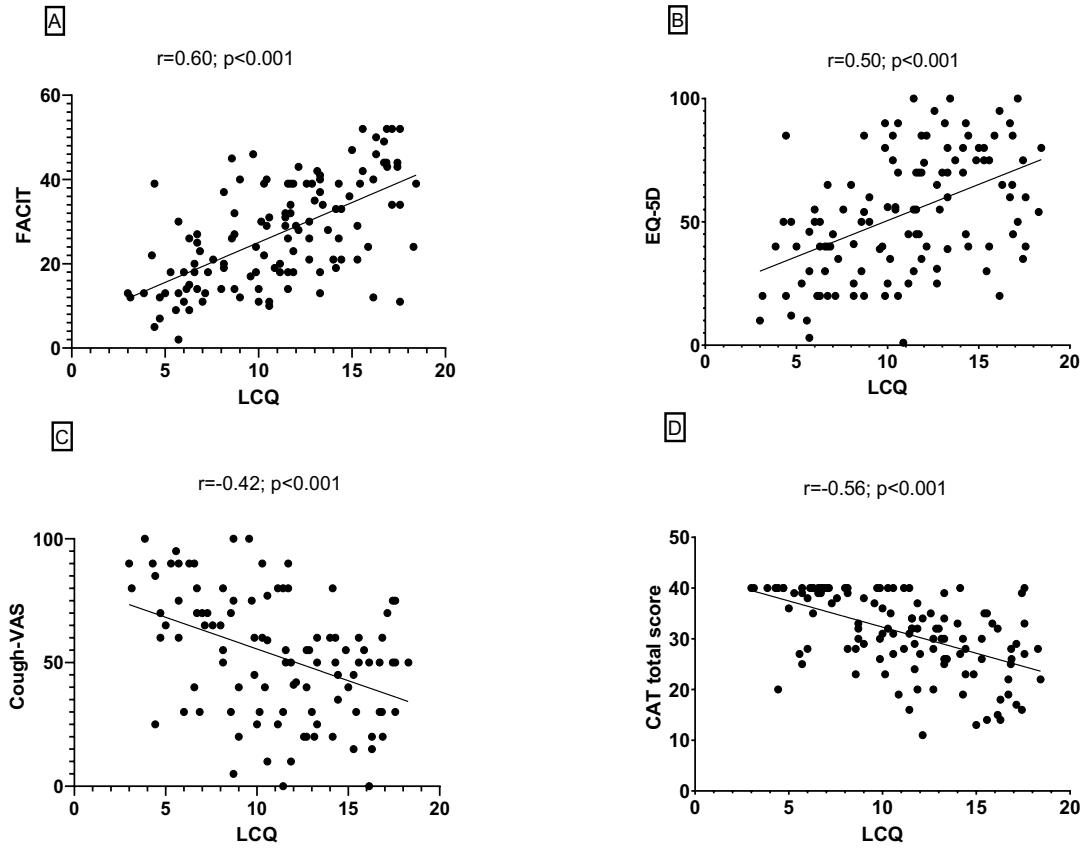


Figure 4.4. Association at the baseline between LCQ and other measures. (A) LCQ *versus* FACIT, (B) LCQ *versus* EQ-5D, (C) LCQ *versus* Cough-VAS, and (D) LCQ *versus* CAT total score.

4.6.2.8 Associations at the baseline between LCQ and CAT (cough item)

As shown in Table 4.8 and Figure 4.5 , the baseline CAT cough is significantly correlated with LCQ, and other measures.

Table 4.8 Association at the baseline between LCQ and CAT (cough item).

At baseline	LCQ	FACIT	Cough-VAS	EQ5D	Sputum scale
CAT cough 1 (n=9)	14.11±3.00	34.80±8.40	17.00±21.32	80.80±9.73	1.50±0.57
CAT cough 2 (n=24)	13.31±3.87	34.95±11.81	43.34±24.50	60.26±24.30	1.50±0.74
CAT cough 3 (n=38)	12.01±3.17	25.31±10.16	51.02±20.02	55.14±22.97	1.37±0.78
CAT cough 4 (n=28)	9.91±3.71	23.00±13.41	56.12±27.11	46.93±26.41	1.37±0.74
CAT cough 5 (n=21)	7.65±3.90	21.76±11.33	66.42±24.72	40.86±21.09	1.24±0.70
Correlation	-0.49	-0.36	0.36	-0.35	-0.10
p-value	P<0.001	P<0.001	P<0.001	P<0.001	P=0.02

4.6.2.9 Association at the baseline between LCQ and CAT (sputum item)

As shown in Table 4.9 and Figure 4.6 , the baseline CAT sputum is significantly correlated with LCQ, and other measures.

Table 4.9 Association at the baseline between LCQ and CAT (sputum item)

At baseline	LCQ	FACIT	Cough-VAS	EQ5D	Sputum scale
CAT sputum 1 (n=8)	14.42±4.49	30.50±11.20	53.33±40.41	57.50±26.32	1.75±1.50
CAT sputum 2 (n=14)	13.24±2.82	32.35±11.77	50.33±20.82	57.14±28.46	1.42±0.66
CAT sputum 3 (n=49)	12.23±3.47	28.30±11.15	50.95±23.16	57.47±23.75	1.50±0.77
CAT sputum 4 (n=35)	9.51±3.82	23.57±14.57	52.49±25.05	46.71±23.66	1.26±0.66
CAT sputum 5 (n=14)	7.82±4.51	20.26±10.26	66.42±29.57	45.41±24.59	1.07±0.26
Correlation coefficient	-0.44	-0.27	0.18	-0.18	-0.20
p-value	P<0.001	P=0.003	P=0.027	P=0.045	P=0.034

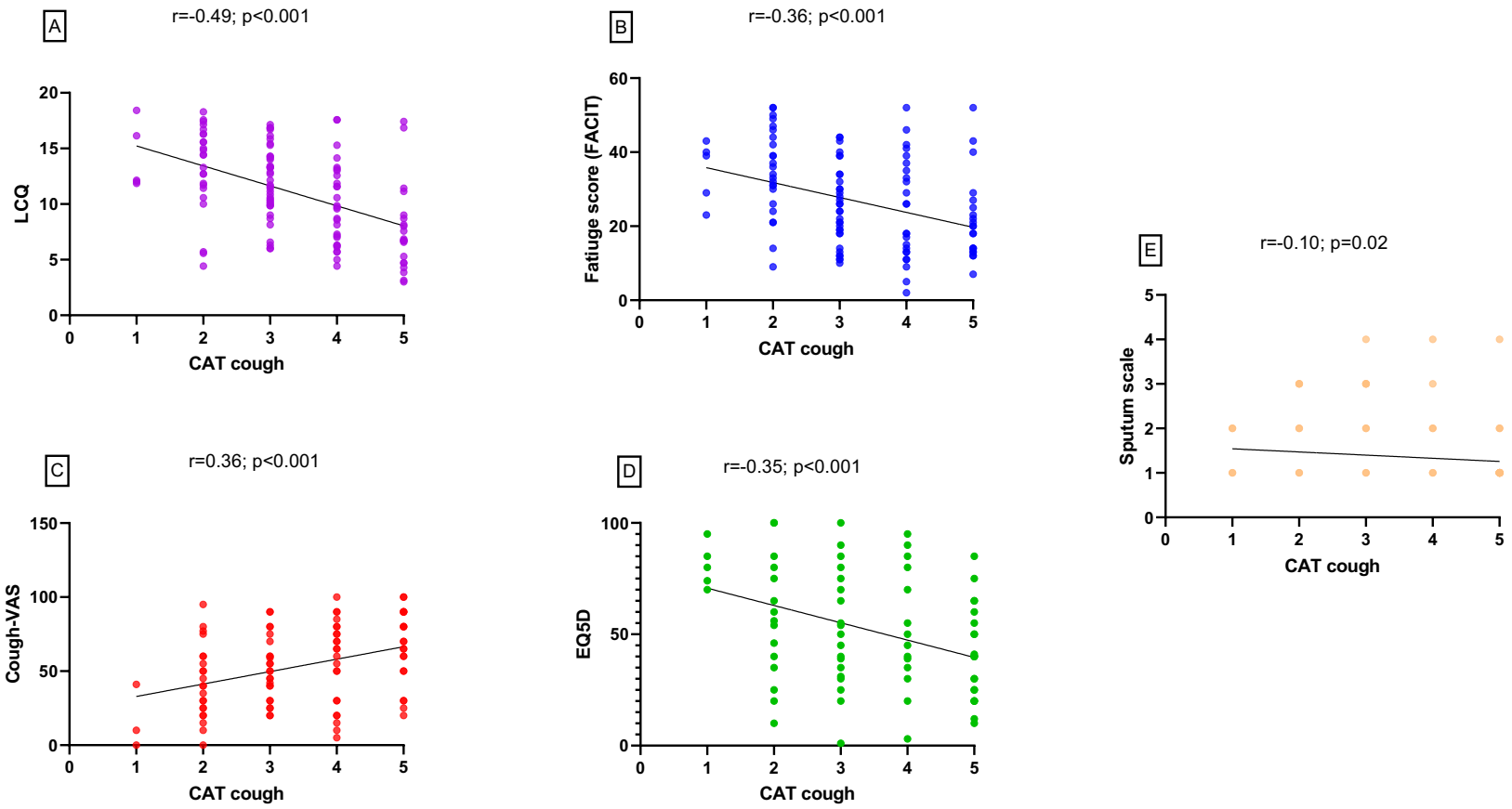


Figure 4.5 Association at the baseline between LCQ and CAT (cough item). (A) LCQ *versus* CAT cough, (B) FACIT *versus* CAT cough, (C) Cough-VAS *versus* CAT cough, (D) EQ-5D *versus* CAT cough, and (E) Sputum scale *versus* CAT cough.

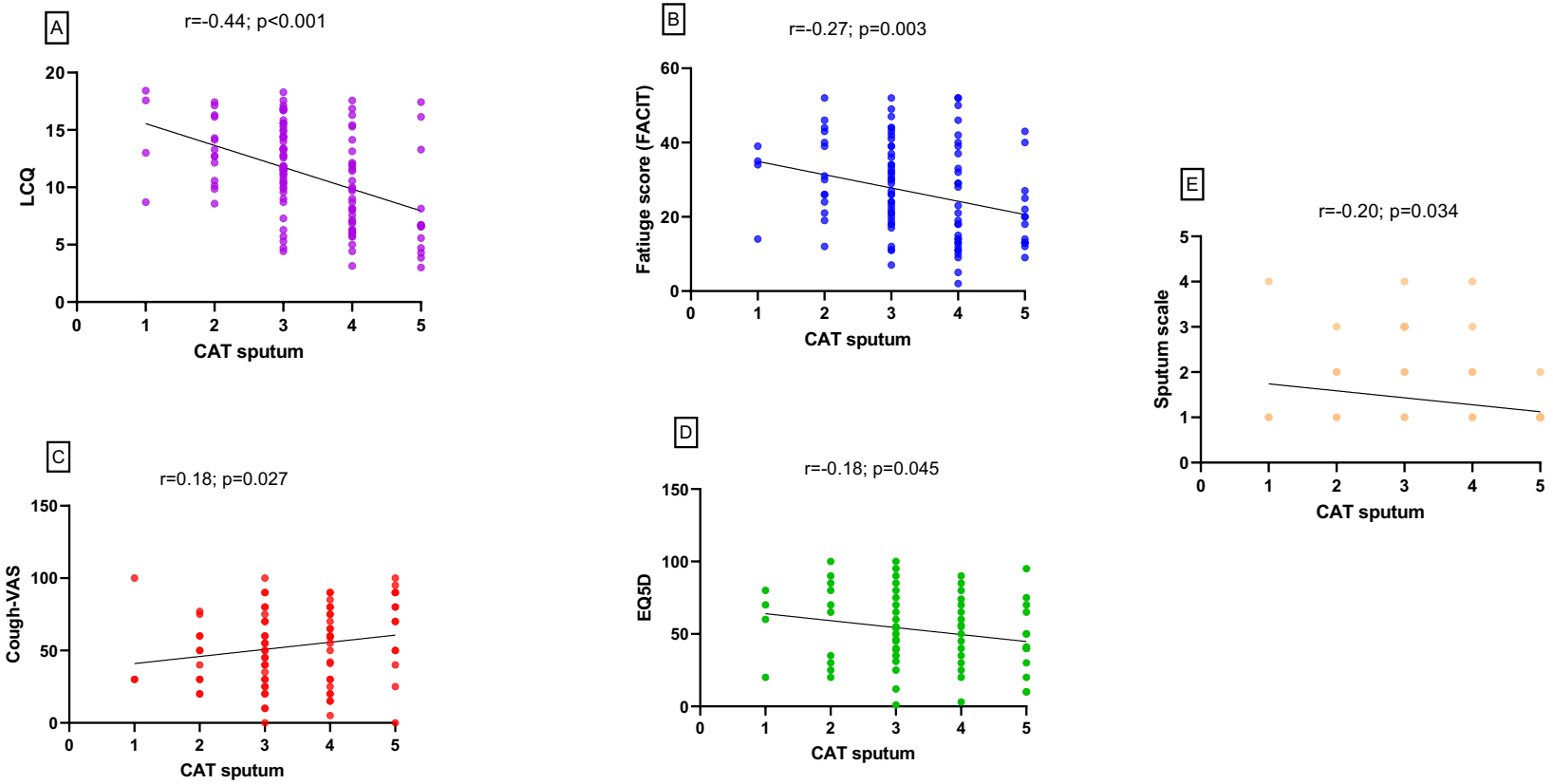


Figure 4.6 Association at the baseline between LCQ and CAT (sputum item). (A) LCQ *versus* CAT sputum, (B) FACIT *versus* CAT sputum, (C) Cough-VAS *versus* CAT sputum, (D) EQ-5D *versus* CAT sputum, and (E) Sputum scale *versus* CAT sputum.

4.6.2.10 Association of change in LCQ based on the CAT cough and CAT sputum

The change in LCQ after three months was significantly correlated with both CAT cough and CAT sputum (p=0.021 and p=0.004) (Figure 4.7 and Table 4.10).

Table 4.10 Mean change in LCQ after three months in CAT cough and CAT sputum.

Association of change in LCQ after three months		
CAT scoring	**CAT cough**	**CAT sputum**
CAT 1 (n=3)	-	0.65±5.90
CAT 2 (n=22)	0.60±4.68	1.04±3.23
CAT 3 (n=37)	0.99±2.80	1.67±2.33
CAT 4 (n=21)	1.70±3.73	1.57±2.89
CAT 5 (n=20)	2.18±3.24	1.73±3.72
Correlation coefficient	0.76	0.90
p-value	0.021	0.004

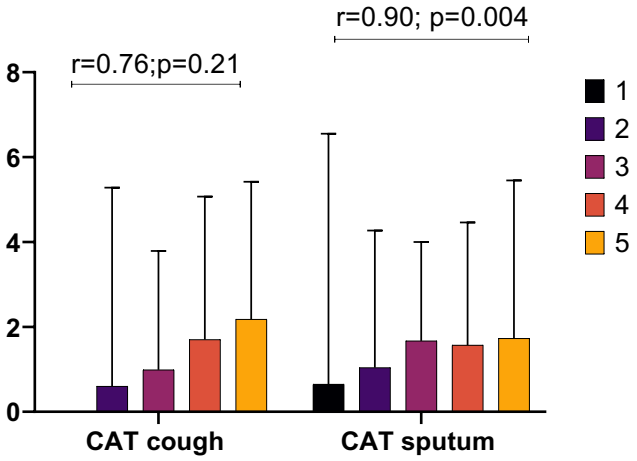


Figure 4.7 Bar chart of the change in LCQ after three months for CAT cough and CAT sputum.

4.6.2.11 Associations of change between measurements after three months

An improvement in LCQ was associated with an improvement in fatigue score (r=0.42, p<0.001), EQ-5D score (r=0.47, p <0.001), CAT score (r= -0.47, p <0.001), and sputum scale (r=0.21; p <0.001) (Table 4.11 and Figure 4.8).

Table 4.11 Correlation of the change between ΔLCQ and other endpoints.

Change	Correlation coefficient (r)	p-value
ΔFACIT	0.42	<0.001
ΔEQ5D	0.47	<0.001
ΔCough-VAS	-0.22	0.050
ΔCAT	-0.47	<0.001
ΔSputum frequency scale	0.21	<0.001

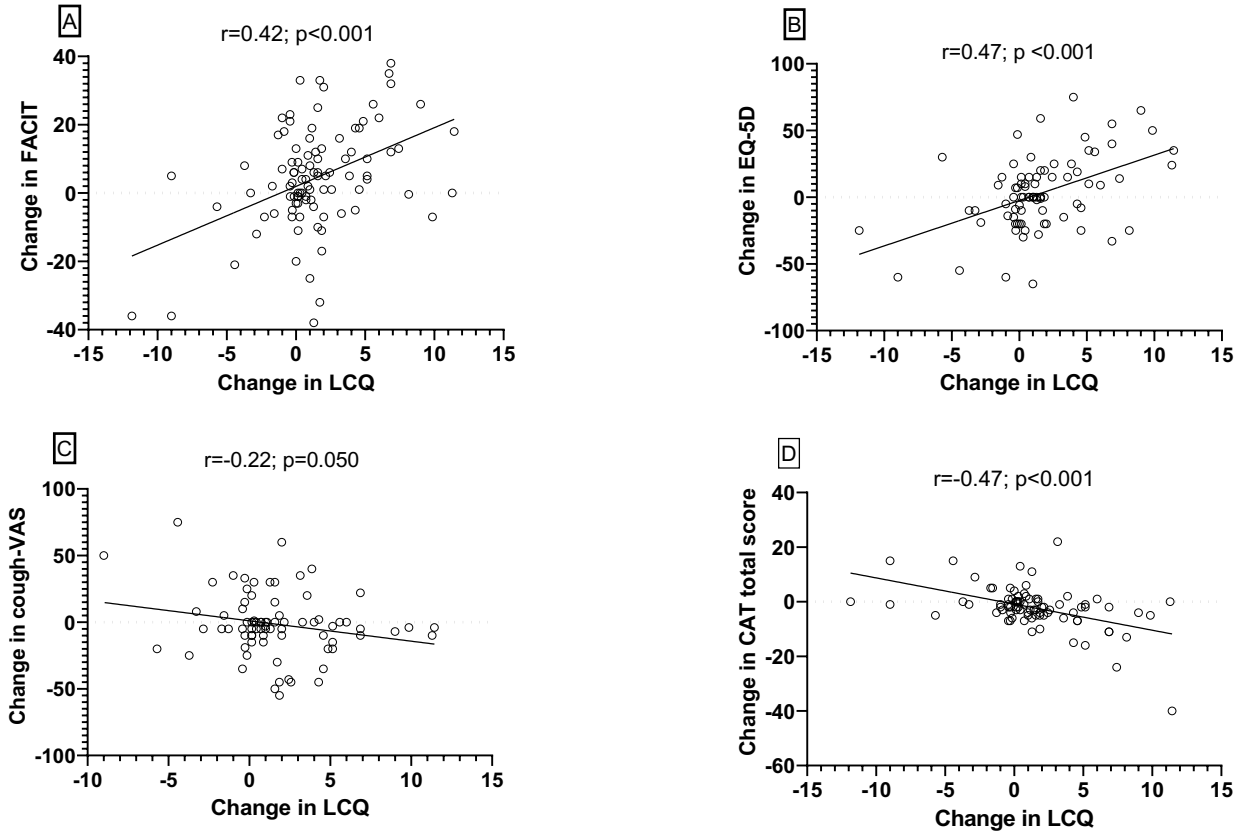


Figure 4.8 Association of the change between LCQ and other measurements. (A) ΔLCQ *versus* ΔFACIT, (B) ΔLCQ *versus* ΔEQ-5D, (C) ΔLCQ *versus* Cough-VAS, and (D) ΔLCQ *versus* ΔCAT total.

4.7 Discussion

4.7.1 Main findings

The main findings of the O-COPD trial show that adding an OPEP device (Acapella) to usual care for three months can significantly improve cough-related quality of life (LCQ). The psychological domain of LCQ was most sensitive to change. The number of COPD exacerbations decreased significantly at the six-week phone call in the OPEP group. Also, daily sputum clearance using the OPEP device was associated with notable improvement in general quality of life (EQ5D), symptoms in COPD patients (CAT), fatigue score (FACIT) and sputum expectoration (Sputum frequency scale) over three months compared to usual care. LCQ results were significantly related to FACIT, EQ5D, sputum scale, Cough-VAS, and CAT score at baseline. LCQ was also associated significantly with CAT cough and CAT sputum items.

4.7.2 Significance of the findings

The primary goal of the O-COPD trial was to assess the impact of using an Acapella on cough-related quality of life. The findings were able to provide information on the relative effect size of OPEP therapy on cough and sputum clearance as well as linking that to fatigue and COPD symptoms, particularly cough and sputum. Considering the current results, it is encouraging to compare the size of effect of OPEP treatment with pharmacological therapy (i.e., Azithromycin) reported by Berkoff et al who found that using Azithromycin for sputum clearance for three months improved LCQ by 1.3 unit (Berkhof, Doornewaard-ten Hertog et al. 2013). Our improvement of 1.03 unit was not quit as big as that seen with azithromycin, but it is interesting to speculate whether the two therapies used together might create a synergistic effect.

It is possible to argue that OPEP therapy is, in general, easier than other airway clearance techniques (i.e., ACBT, huffing cough) (Hristara-Papadopoulou, Tsanakas et al. 2008). There is a small body of literature that compared the impact of different OPEP devices in COPD reporting that these devices are effective in controlling COPD symptoms including sputum clearance (Cegla, Jost et al. 2002, Wolkove, Baltzan et al. 2004, Aggarwal, Shaphe et al. 2010, Sethi, Yin et al. 2014, Svenningsen, Paulin et al. 2016, Nicolini, Mascardi et al. 2018). However, information about patient selection, frequency of OPEP use, direct impact of OPEP on cough outcome and/or quality of life were not reported.

A clinical trial of a similar size compared an OPEP device with a sham device three times a day for three months in COPD patients reported no benefit with regard to breathlessness, but it showed small improvements (5 cm H_2O) in inspiratory muscle strength. Unlike our trial (the O-COPD), this one recruited COPD patients who were not daily sputum producers (Daynes, Greening et al. 2021).

The process of doing this research started with exploring patient selection, current prescriptions, and the physiotherapist attitudes toward OPEP devices (Barker, Laverty et al. 2017). Interesting data from Barker et al (Barker, Laverty et al. 2017) showed that the routine clinical practice relied more on medication (i.e., Carbocisteine) over OPEP devices with a 100-fold difference between prescribing medications and OPEP devices (Barker, Laverty et al. 2017). However, over the years (the report covered the period from 2013 to 2015) there was an increased rate (~ 80%) in prescribing OPEP devices in the primary care setting (Barker, Laverty et al. 2017). This is a good indicator that the clinical consensus about the value of non-pharmacological therapies within COPD management is growing. Interestingly, the largest impact on our data is likely seen in COPD patients with frequent sputum production.

Those patients, to some extent, represent a middle group. This might not be the case in COPD patients who are rarely or excessively produce sputum. To address this, in the current study, patient selection was guided by self-reported descriptions of sputum as well as the sum of CAT cough and sputum items ≥5 out of 10. These brief descriptions of the recurrence of sputum production are the best available method to identify the clinical phenotype in such a heterogeneous condition (descriptions were provided in method section), but we accept that better approaches may emerge in the future. Importantly, our analysis at the baseline demonstrated that the use of the first two CAT items is supported by the correlations seen between the score for these items (cough and sputum) and LCQ, EQ-5D, FACIT, sputum scale, and Cough-VAS. Although the majority were regular sputum producers, formal phenotyping based on the level and severity of cough and sputum production in COPD must be considered in designing a personalised treatment plan, as well as facilitate targeting the right people for the right treatment.

We also found an association between cough-related quality of life, fatigue, and sputum clearance. These results reflect those of Chate et al (Choate, Pasquale et al. 2020) who also found that coughing and sputum production contribute to fatigue and sleep disturbance in COPD patients (Choate, Pasquale et al. 2020). Treating and managing cough in COPD patients is an important aspect, and it should be addressed as part of the comprehensive COPD management program. Quantifying that improvement in objective cough outcome, as well as cough variation, and its association with fatigue as well as sleep movements overnight are present in chapters 5 and 6.

Linking our results to previous studies that discussed OPEP devices in COPD (Cegla, Jost et al. 2002, Wolkove, Baltzan et al. 2004, Aggarwal, Shaphe et al. 2010, Sethi, Yin et al. 2014, Svenningsen, Paulin et al. 2016, Nicolini, Mascardi et al. 2018) it would be possible to say that

acapella device to some extent produce the same benefit as the other OPEP devices, but it may not be generalized as there are some differences between OPEP devices, including the device relative efficacy and optimal mechanical performance (Alghamdi, Barker et al. 2020). In particular, the Acapella exercise saves more time than other airway clearance techniques, and it is associated with the most significant improvements in clinical outcome compared to other OPEP devices (Alghamdi, Barker et al. 2020).

4.7.3 Clinical implications of O-COPD

The use of OPEP devices remains a controversial and neglected area in COPD. Possible arguments can be mentioned. First, evidence that support OPEP devices general efficacy and/ or their relative effectiveness still inconclusive. Second, there is no optimal strategy for OPEP device use, for example, if the patient can use them regularly or as required. Third, there are still no established selection criteria where OPEP devices can be recommended as standard treatment for COPD. Finally, the available evidence about their longer-term effect, acceptability, and relative value to other interventions still undiscovered.

In the NICE guidelines (1.2.40 and 1.2.99), sputum in COPD is currently recommended to be treated with pharmacological therapy or ACBTs, but not with OPEP devices (Hopkinson, Molyneux et al. 2019). Although cumulative evidence suggests a positive impact from the short-term use of OPEP devices in people with COPD (Alghamdi, Barker et al. 2020, Daynes, Jones et al. 2021), little is known about the long-term impact or patient selection. In other words, it is not yet clear whether clinical consensus exists regarding OPEP recommendations within COPD management guidelines (Qaseem, Wilt et al. 2011, Barker, Laverty et al. 2017, Vogelmeier, Criner et al. 2017, Hopkinson, Molyneux et al. 2019). The rationale for this can be the evidence deficits in providing clear recommendations for OPEP devices use,

particularly with COPD patients for whom sputum production is a concern. Another rationale is that the paucity of clinical trials that have evaluated the long-term impact of OPEP devices in COPD patients with frequent sputum production and/or have evaluated whether OPEP devices have an impact on quality of life in particular COPD phenotype.

In the context of COPD, an important contribution of the current study is that it adds knowledge about OPEP device effectiveness in improving quality of life and airway clearance in conjunction with standard care, which may update the current clinical practice with high-level evidence about OPEP device with COPD. The study introduces a possible strategy to identify patient selection who frequently produce sputum rather than people who are excessively or rarely bothered by sputum. Also, optimising usual care can lead to improved health-related quality of life both specific and general, minimise the burden of the COPD symptoms. Consequently, the treatment cost will fall, and the quality of care will improve.

4.7.4 Limitations of the study

When interpreting the results of this study, some limitations must be acknowledged. The duration of the study was not long enough to know if OPEP device usage for a longer period of time (i.e., 6 months, 12 months) would provide a clinically significant impact on treatment cost or other patient outcomes such as COPD exacerbations. Even though our data showed a significant reduction in AECOPD in the OPEP group compared to the usual care on the six-week phone calls, this is still a high rate of AECOPD in stable COPD. These results may be due to the fact that the perspective on developing exacerbations differed between participants. In addition, the information gathered over the phone was tied to AECOPD events and the use of medications rescue packs. the AECOPD should be followed for a longer period of time (i.e.,

1 year). Additionally, there were no placebo or sham device used in this trial, which limited our ability to detect any placebo effects.

The COVID-19 pandemic has made video conferencing and video links a viable option for training on acapella instead of face-to-face training. This has no impact on the treatment process and has shown that remote treatment via telehealth can benefit some patients. The success of this approach suggests that for some people the offer of remote support to perform sputum clearance may enhance access (Alghamdi, Rajah et al. 2021). Six weeks phone call have demonstrated that all participants watched the video link at least once before doing Acapella treatment or ACBT, but future studies could explore whether enhanced remote support improved delivery of the interventions.

Our data are from a single centre; when the O-COPD was planned, it was intended to use more than one centre, but this proved impossible during COVID-19 pandemic restrictions, and thus we missed exploring the impact of OPEP device in different geographical locations with different COPD population and lacked the additional robustness that additional centres would have conferred. Of necessity, there was no placebo, but usual care group received ACBT exercise and were encouraged to preform it three times a day. ACBT is not usually performed by patients in routine care. It could be possible that the OPEP treatment arm had an double effect (Acapella + ACBT) compared to the usual care alone, as we already have evidence that an ACBT exercise is an effective way to improve airway clearance, cough efficiency, and health-related quality of life in the COPD population (Osadnik, McDonald et al. 2012, Shen, Li et al. 2020). Future studies could explore OPEP + ACBT *vs* OPEP alone though they require a larger sample size. Clearly a trial of that would need to capture both clinical effects and patient inconvenience associated with undertaking the therapy. In the context of future research, it

might be worthwhile to investigate the differences and similarities between OPEP devices using direct comparison of two devices in COPD population (i.e., Acapella versus Aerobika). It is also possible that OPEP devices work with certain groups but not with others, so it would be interesting to evaluate that in different COPD phenotypes or different levels of airflow obstructions. Adding to that there is a call for long term clinical trials with bigger sample size to evaluate the impact of OPEP devices on the recurrent COPD exacerbations and/or health economics.

4.8 Conclusion.

Results from the O-COPD trial, coupled with the previous evidence from clinical trials increase confidence regarding the long-term effectiveness of OPEP devices in treating sputum and cough aspects in stable COPD patients. COPD patients with sputum production who received OPEP treatment for three months, compared to the usual care, demonstrated better disease management and improvement in general and cough-related quality of life (LCQ). The findings suggest that adding the OPEP device is effective in optimising the usual care and, perhaps, can be the new mode of usual care in managing cough and sputum production in COPD patients. Larger and longer clinical trials are required to guide the long-term use of OPEP and patient selection.

5 Relationship between objective cough monitoring and actigraphy sleep movements: Cross-sectional data from the O-COPD trial

5.1 Abstract

Rationale: Limited objective data are available about cough characteristics and frequency in people with COPD, nor about the contribution of cough events to sleep disturbance and their impact on sleep efficiency. To address this, we measured cough frequency with objective monitoring and assessed the relationship between nocturnal cough frequency and sleep disturbance by actigraphy in people with COPD and regular sputum production.

Methods: This is a sub-study of the baseline population from the O-COPD trial (ISRCTN44651852) described in the previous chapter, which recruited stable patients with COPD reporting a productive cough (daily or most days in the preceding month) and scoring ≥5 out of 10 in the first two items (cough and sputum) of the CAT score. Cough frequency was measured using the Leicester Cough Monitor (LCM). Sleep parameters and body movements were measured using the DynaPort MoveMonitor (McRoberts BV, The Hague, Netherlands). The participants were asked to document the time went to sleep. Cough frequency was reported as number of coughs per 24 hrs. Body transition defined as a description of the level of changing from one position to another positions. Data are presented as mean and standard deviation or geometric mean ± log SD. Additional descriptive analysis provided based on the sputum scale, CAT cough item, and CAT sputum item from the COPD assessment tool (CAT).

Results: 45 COPD participants (OPEP n=25, UC n=20) were recruited; age 63±10 years, female 33.35%, ex-smokers 75.6%, FEV_1 1.18 [0.77-1.65] (L), 31 (68%). In all participants,

cough was more frequent during the day than at night (Geometric mean± Log SD; day 86±0.37 versus night 59 ± 0.52). Cough frequency from LCM was significantly associated with Leicester cough questionnaire (LCQ) ($r= -0.60$; $p < 0.001$). Nocturnal cough frequency was significantly associated with time out of bed (Pearson correlation; $r= 0.72$, $p<0.001$), and total body transitions ($r=0.857$, $p<0.001$).

Conclusion: COPD patients cough more during the day than at night. Night-time cough frequency is a potential cause of sleep disturbance as manifest by more frequent body movements. Combined subjective and objective monitoring of cough in COPD is feasible and provides a better understanding regarding the repeatability of the cough in COPD with cough and frequent sputum production.

5.2 Introduction

In the previous chapter (The O-COPD Trial), we described our plans to collect data for objective cough monitoring and sleep movements overnight for a subset group from the O-COPD Trial. Despite the fact that the main finding of the O-COPD trial concluded that OPEP therapy improves cough symptomatology in COPD, one of the key reasons for this study was to investigate the relationship between subjective and objective cough measurements to confirm the hypothesis *"the worse the symptoms (CAT cough and CAT sputum), the worse cough-related quality of life (LCQ)."* This sub-study was conceived to quantify the symptoms (through objective monitoring), since subjective measurements inform both about the severity of cough and the patient's perception of cough whereas objective measures inform about the former alone. Furthermore, subjective measures cannot reliably measure cough while asleep though they could give insight into sleep disturbance.

Another rationale for writing this chapter is the fact that coughing (with or without sputum) is happening both during the day and at night. Coughing during the night may be associated in-bed movements, which may lead to or be reflective of getting out of bed or sleep disturbance. COPD patients who frequently produce sputum have rarely been studied for this phenomenon, and clinical outcomes have mostly been reported as subjective assessments (Hartman, Prinzen et al. 2015). There is little research on the relationship between cough, sputum production, sleep disruption, and fatigue in COPD patients. However, to the best of the current author's knowledge, the study protocol, which includes tracking cough and sleep actigraphy in the same night, is original and has never been published before. By doing so, we provide a cross-sectional data to fill this gap and inform current literature. Thus, the objectives of the current chapter are:

- Describe cough frequency and actigraphically determined sleep movements in COPD participating in the O-COPD trial.
- Assess the correlation of cough frequency at the baseline with the LCQ, FACIT, Cough-VAS, EQ5D, and Sputum scale.

5.3 Methods

Full explanations of the methods have been described in chapter 3.

5.3.1 Participants

This chapter presents a cross-sectional study (sub-study from the O-COPD Trial registration: ISRCTN44651852).

5.3.2 Data recording

5.3.2.1 Cough monitoring

The Leicester cough monitor (LCM) was used to monitor the cough frequency. The LCM is an ambulatory objective cough monitor developed by Birring et al. (Birring, Fleming et al. 2008). It uses a voice trace system combined with an algorithm to record and detect cough frequency in 24-h (day and night). During the recording, participants were instructed to worn LCM and continue their usual activities. When the cough monitors were returned, the recordings were downloaded, stored, and analysed by me at respiratory medicine department in King's College Hospital. A written instruction and patient diary were also given with the monitor, and the participants asked to record bedtime and waking up time. Nighttime cough was defined as the cough frequency during the sleeping time per individual. Daytime cough was defined as the cough frequency during the waking time per individual. Cough frequency expressed as number of coughs per 24 hours (24h cough frequency) and coughs per hour.

Photos and instructions for participants were described in Appendix 6 and Appendix 7. Full details about LCM were provided in Chapter 2.

5.3.2.2 Actigraphy and sleep disturbance

DynaPort (McRoberts, MoveMonitor) was used to monitor the night's rest and body movements (body transitions) during sleep. It provides reports about the night's rest parameters. Participants were instructed to wear the DynaPort and continue their usual activities. When the monitors were returned, data were downloaded to DynaPort software. The software processing data and provide a sleep movement report per patient. Written instructions and patient diary also were given with the monitor. Instructions for participants were described in Appendix 8. Full details about DynaPort were provided in chapter 2

Table 5.1 Definitions of night's rest parameters.

Parameters	Unit of measure
Night rest time (night start, night end)	Time
Lying down	Time
Movement duration	Proportion of the movement from the total night rest
Getting out of bed	Time period and frequency
Body postures (left, right, prone, supine, upright)	Time and proportion from the total body postures
Body transitions (small, medium, large, extra-large, and sitting)	Frequency, and transitions/hour

5.3.3 Data validation

Data validation was in accordance with the previous literature (Birring, Fleming et al. 2008, Gloeckl, Damisch et al. 2015). A cough measurement was considered valid if the patients wore the cough monitor for a full 24 hours (Birring, Fleming et al. 2008) and the DynaPort monitor for 48 hours, two consecutive days and nights (Gloeckl, Damisch et al. 2015). Paired data were obtained at the baseline and three months later of the O-COPD trial.

5.3.4 Procedures

The participants were asked to collect measurements taken during three consecutive days/nights, as per study protocol. Both monitors were given to the same participants at the same time. The monitors were set up at the clinic. After that, the patients were given the monitors to perform the cough recordings and the night's rest monitoring at home. Then, the patients were asked to return or post the monitors to the clinic after completing the measurements. A help telephone line (Monday to Friday; 9:30 am to 5:00 pm) was also provided during the study if the patients' needs any help or faced any challenges. Beside the primary endpoint, LCQ, there were some questionnaires (FACIT, EQ5D, Cough-VAS, CAT, sputum frequency scale) the participants were expected to complete as baseline measure for the O-COPD trial.

5.3.5 Statistical analysis

Data analysis was performed using SPSS version 26.0 (IBM, SPSS, Illinois, USA) and Prism 9.2.0 (GraphPad Software Inc, California, USA). The baseline characteristics are expressed as mean and standard deviation, median and interquartile ranges, frequencies and proportions, as appropriate. Distribution of the data checked by the normality tests. Logarithmic transformation was used for skewed data to normalise the distribution, and the data were expressed as geometric means (GEM) and logarithmic standard deviation (LogSD) (Sumner, Woodcock et al. 2013). If that data still not normally distributed after the transformation, the median and IQR were used to present the data. Pearson correlation tests were used to assess the relationship between continuous variables, and Spearman's rho correlation test if the data were categorical. The sample size of this study was based on the objective cough measurements described in chapter 2. I also performed a descriptive analysis using the sputum frequency scale, and categorized patients as DSPs or NDSPs. Furthermore, I

summarized the data based on CAT cough and CAT sputum. P-value < 0.05 considered statistically significant.

5.4 Results

5.4.1 Baseline characteristics

Out of 122 enrolled in the O-COPD trial, 45 patients were agreed/consented to participate in this sub-study: they had age 62.11±10.30 years, 33.35% female, 75.6% ex-smokers, and FEV_1 1.18 [0.77 to1.65] (L). The mean score of total LCQ was 11.84±3.96, Cough-VAS 51.54±24.64, and CAT total 31.88±9.07 (Table 5.2).

Table 5.2. Baseline characteristics for participant agreed to take the LCM and DynaPort monitors (n=45).

Characteristics	Mean ±SD, N (%), Median (IQR) **No objective monitoring (n=77)**	Mean ±SD, N (%), Median (IQR) **Objective monitoring (n=45)**
Age	63.28±10.31	62.11±10.30
Gender (Female)	34 (44%)	15 (33.35%)
Pack per year	20 (12 – 25)	15 (12- 30)
Smoking history		
Smoker	10 (13%)	11(24.4%)
Ex-smoker	67 (87%)	43 (75.6%)
Airway obstructions (GOLD) grades		
COPDI	8 (10.4%)	4 (8.95%)
COPDII	21 (27.3%)	8 (17.8%)
COPDIII	28 (36.4%)	22 (48.9%)
COPDIV	20 (26%)	11 (24.4%)
AECOPD last year		
0	n/a	n/a
1	37 (45%)	28 (70%)
2	10 (12%)	5 (12%)
3	7 (9%)	2 (4%)
>3	12(15%)	6 (14%)
Lung volumes		
FEV_1 Litre§	1.03 [0.78 -1.49]	1.18 [0.77-1.65]
FEV_1 % predicted§	37[25-61]	40.50 [26-52]
FVC Litre §	2.84[2.37-3.51]	3.16[2.24-3.78]
FVC % §	88[71-98]	82[70-94]
FEV_1/FVC % §	36[27-47]	37[29-46]
TLC%§	136[120-147]	132[118-141]
RV% §	207[163-255]	211[135-2578]
Questionnaires		

LCQ total score	11.14±4.02	11.84±3.96
Physical	4.28±1.49	4.71±1.58
Phycological	4.14±1.65	4.42±1.61
Social	2.42±1.00	2.57±1.17
Cough-VAS	53.87±25.62	51.54±24.64
CAT total	32.00±8.62	31.88±9.07
Sputum frequency Scale	1.33±0.70	1.43±0.75

Note: SD, standard deviation; interquartile range; GOLD, Global initiative for chronic obstructive lung disease; FEV1, Forced expiratory volume in one second; FEV1%; predicted force expiratory volume in one second; FVC, forced vital capacity; FVC%, predicted forced vital capacity; TLC%, predicted total lung capacity; RV%, predicted residual volume.

§ the data reported as median and IQR.

5.4.2 Cough and sleep actigraphy characteristics

5.4.2.1 Cough and sleep actigraphy variation

Table 5.3 showed the cough and sleep actigraphy variation. The geometric mean ± logSD of 24-h cough frequency in all participants was 134±0.34. The participants coughed more in the daytime than the nighttime (86 ±0.37 coughs versus 59 ±0.52 coughs).

Table 5.3. Summary of cough frequency and sleep actigraphy variation in all participants at the baseline.

Cough variable †	**All (n=45)**
24-h cough frequency, n	134±0.34
Daytime cough frequency, n	86±0.37
Nighttime cough frequency, n	59±0.52
Total cough per hour	8.9±0.34
Daytime cough per hour	5.9±0.35
Nighttime cough per hour	3.9±0.48
Sleep movement parameters	**All (n=45)**
Duration night's rest, hours	8.20±3.27
Lying down, hours	10.25±3.32
Move intensity, g	0.06±0.062
Total Movement duration, mins	5.97±6.39
Getting out of bed, n	2.60±1.35
Body postures, hours	
Left	1.47±1.81
Right	1.91±1.84
Prone	1.47±2.71
Supine	2.10±1.77
Upright	0.48±0.73
Out bed, min	0.25±0.47
Transitions, n	
Small	16.51±11
Medium	3.80±3.98

Large	1.92±2.03
Extra large	1.02±1.12
Sitting	8.48±1.12
Total transitions	32.1±18.24
Total Transition per hour	3.98±2.05

Note: † Data are presented as GEM mean ±log SD; n: number; g: gram.

5.4.2.2 Correlation between cough events during the daytime versus nighttime

The correlation between daytime and nighttime coughs was r=0.77, and the p<0.001, meaning that the participants most likely had a constant cough (Figure 5.1).

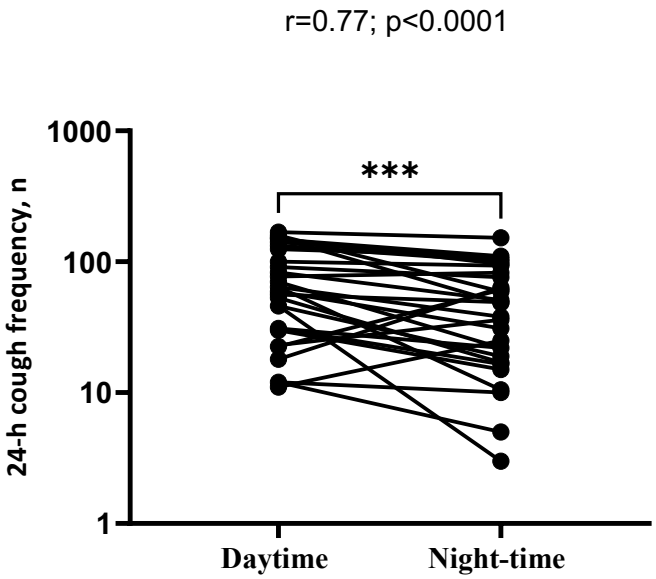


Figure 5.1 Correlation between coughs variation during the daytime and nighttime.

5.4.2.3 Association between 24h cough frequency and other measurements at baseline

Table 5.4 show the results of corelation of 24h cough frequency (day and night) and other measurements. The correlation presented for both cough frequency and coughs per hour. In

general, 24h cough frequency correlated with LCQ total score (r=-0.60; p=0.021), Cough-VAS (r=0.49; p=0.004), FACIT score (r=-0.38; p=0.025), CAT score (r=0.55; p=0.001), sputum frequency scale (r=0.53; p=0.001), and total body transitions (r=0.37; p=0.075).

Table 5.4. Correlation of cough frequency at baseline and other measures.

Questionnaires	Cough parameter	Correlation coefficient	p-value
LCQ	24h cough frequency	-0.60	**<0.001**
Psychological domain	24h cough frequency	-0.58	**<0.001**
Social domain	24h cough frequency	-0.44	**0.009**
Physical	24h cough frequency	0.26	0.137
EQ-5D	24h cough frequency	-0.09	0.583
Cough-VAS	24h cough frequency	0.49	**0.004**
Fatigue score (FACIT)	24h cough frequency	-0.38	**0.025**
CAT total	24h cough frequency	0.55	**0.001**
CAT cough	24h cough frequency	0.55	**<0.001**
CAT sputum	24h cough frequency	0.44	**0.008**
CAT sleep	24h cough frequency	0.05	0.772
CAT energy	24h cough frequency	0.17	0.318
Sputum frequency scale	24h cough frequency	0.53	**0.001**
Times out of bed, n	24h cough frequency	0.18	0.576
Time spent out of bed, mins	24h cough frequency	0.14	0.675
Small body transitions, n	24h cough frequency	**0.48**	**0.017**
Medium body transitions, n	24h cough frequency	0.01	0.969
Large body transitions, n	24h cough frequency	0.24	0.444
Extra-Large body transitions, n	24h cough frequency	0.23	0.453
Sitting body transitions	24h cough frequency	0.21	0.498
Total body transitions, n	24h cough frequency	0.37	0.075

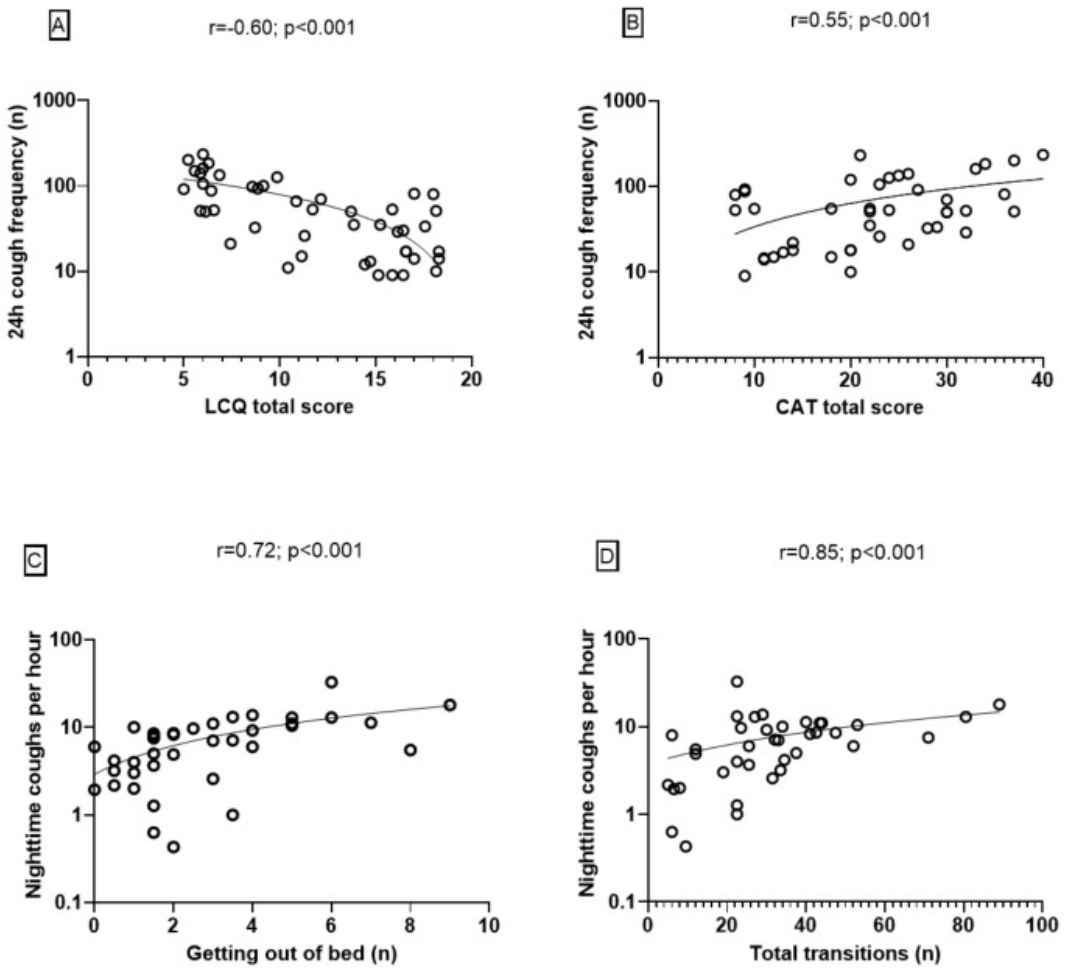


Figure 5.2 Correlation at baseline between study outcomes. (A) correlation of 24h cough frequency with LCQ total score; (B) correlation of 24h cough frequency with CAT total score; (C) correlation of nighttime coughs per hour with getting out of bed; and (D) correlation of nighttime coughs per hour with total transitions.

5.4.3 Additional descriptive analysis for cough frequency based on the CAT items

5.4.3.1 Cough variation and sleep actigraphy based on CAT cough

Table 5.5 show cough variation based on CAT cough. There was a significant correlation between increasing cough frequency and worse CAT cough score. Otherwise, there were no significant differences in actigraphy and sleep movements (Table 5.7).

Table 5.5 Cough variation based on the CAT cough item.

	24-Cough frequency	Daytime coughs, n	Nighttime coughs, n
CAT cough = 1 (n=2)	68 [44 to 92]	57 [44 to 70]	11 [1 to 20]
CAT cough =2 (n=3)	53 [49 to 70]	46 [31 to 53]	17 [3 to 22]
CAT cough =3 (n=11)	102 [17 to 218]	64 [12 to 159]	51 [5 to 93]
CAT cough =4 (n= 6)	145 [47 to 288]	95 [18 to 168]	56 [16 to 152]
CAT cough =5 (n=12)	240 [36 to 320]	133 [11 to 288]	73 [15 to 278]
Correlation's coefficient	0.20	0.17	0.17
p-value	p<0.001	p<0.001	p<0.001

Note: Data presented as median and IQR.

5.4.3.2 Cough variation and sleep actigraphy based on CAT sputum

Table 5.6 show the cough variation based on CAT sputum. There was a significant trending correlation between cough frequency and worse CAT sputum score. Otherwise, there were no significant differences in actigraphy and sleep movements (Table 5.8).

Table 5.6 Cough variation based on CAT sputum.

	24-Cough frequency	Daytime coughs	Nighttime coughs
CAT sputum =2 (n=3)	47 [18 to 70]	31[12 to 53]	17 [5 to 17]
CAT sputum =3 (n=13)	92 [22 to 233]	64 [12 to 159]	36 [3 to 100]
CAT sputum =4 (n= 10)	113 [44 to 320]	77[18 to 168]	63 [15 to 152]
CAT sputum =5 (n=8)	240 [36 to 288]	125 [11 to 288]	78 [19 to 278]
Correlation coefficient	0.17	0.15	0.22
p-value	p=0.013	p=0.023	p=0.006

Note: Data presented as median and IQR.

Table 5.7 Additional analysis for actigraphy and sleep movements based on CAT cough.

	Duration night's rest, hours	Lying down, hours	Total Movement duration, mins	Time out bed, min	Getting out of bed, n	Total transitions	Small	Medium	Large	Extra large	Sitting	Transitions per hour
CAT cough =2 (n=5)	7.91±3.37	10.2±3.28	4.11±6.60	0.10±0.11	2.57±0.86	28.62±14.30	12.75±10.35	5.16±3.39	1.83±2.68	1.12±1.85	6.00±3.46	3.61±1.93
CAT cough =3 (n=15)	8.51±3.91	8.38±2.1	5.9±4.60	0.13±0.19	2.50±1.94	29.95±14.10	14.29±11.53	3.29±2.53	2.25±1.57	1.25±1.37	8.75±6.42	3.43±1.67
CAT cough =4 (n=9)	8.73±4.71	10.47±2.62	9.80.344	0.41±0.84	3.80±1.10	26.80±14.25	14.75±27.57	1.00±0.64	1.75±2.80	1.00±0.95	7.00±4.41	3.88±3.38
CAT cough =5 (n=4)	8.60±1.73	10.52±0.47	8.24±9.20	0.26±0.25	2.08±2.65	44.08±27.00	24.33±10.50	5.00±2.89	1.50±1.04	1.00±0.70	10.75±12.10	5.31±2.39
Correlation coefficient	-0.21	-0.15	0.38	0.14	0.03	0.28	0.14	0.15	0.15	0.15	0.13	0.13
p-value	0.23	0.43	0.06	0.46	0.85	0.13	0.46	0.42	0.43	0.42	0.47	0.49

Table 5.8 Additional analysis of actigraphy and sleep movements based on CAT sputum.

	Duration night's rest, hours	Lying down, hours	Total Movement duration, mins	Time out bed, min	Getting out of bed, n	Total transitions	Small	Medium	Large	Extra large	Sitting	Transitions per hour
CAT sputum =2 (n=5)	6.50±1.66	9.85±3.14	3.19±4.31	0.04±0.04	0.87±0.62	11.66±9.30	5.00±6.93	0.66±0.76	0.50±0.68	0.16±0.28	5.50 ±0.46	1.97±1.03
CAT sputum =3 (n=15)	9.27±3.87	10.73±2.88	6.68±6.26	0.21±0.29	2.71±1.75	34.53±16.10	16.00±8.53	4.20±4.08	2.50±2.37	1.33±1.21	10.40±9.42	3.97±1.69
CAT sputum =4 (n=9)	7.88±3.55	7.93±1.99	7.33±9.63	0.67±0.95	3.50±2.38	36.00±24.25	20.58±17.03	5.10±6.21	1.85±2.22	1.08±1.56	5.40±3.96	4.88±2.80
CAT sputum =5 (n=4)	7.66±1.99	10.64±4.25	8.24±9.20	0.04±0.04	1.37±0.85	31.12±12.71	16.62±9.00	3.62±1.54	1.75±1.19	0.75±0.70	5.75±1.84	4.60±1.85
Correlation coefficient	0.120	-0.213	0.184	0.067	0.010	0.290	0.135	0.060	0.114	-0.179	0.268	0.343
p-value	0.50	0.26	0.33	0.70	0.96	0.12	0.48	0.75	0.55	0.35	0.16	0.06

5.4.4 Additional descriptive analysis based on the sputum frequency scale

5.4.4.1 Cough variation and sleep actigraphy based on the sputum frequency scale

Participants were categorised as daily sputum producers (DSP) and not daily sputum producers (NDSP). There were no statistically significant differences between groups for coughing, but there were for sleep actigraphy (Table 5.9).

Table 5.9 Additional analysis of cough frequency and sleep actigraphy based on sputum scale.

Cough variables†	**DSP (n=31)**	**NDSP (n=14)**	**p-value**
24-h cough frequency, n	145±0.30	116±0.37	0.37
Daytime cough frequency, n	90±0.34	79±0.36	0.67
Night-time cough frequency, n	69±0.41	43±0.35	0.22
Total cough per hour	9±0.31	9±0.39	0.84
Daytime cough per hour	6±0.32	6±0.36	0.77
Nighttime cough per hour	4.7±0.34	2.5±0.38	0.15
Sleep actigraphy	DSP(n=31) Mean±SD	NDSP(n=14) Mean±SD	p-value
Duration night's rest, hours	8±3.50	8.7±3.29	0.65
Lying down, hours	9.6±2.8	11±2.8	0.59
Move intensity, g	0.07±0.07	0.05±0.02	0.22
Total Movement duration, mins	6.4±7.11	5.28±6.1	0.44
Getting out of bed, n	3.1±2.47	2.4±1.7	0.02
Body postures, hours			
Left	1.5±1.7	1.2±1.7	0.68
Right	1.7±1.6	2.1±2.2	0.66
Prone	1.6±3.2	0.90±1.43	0.33
Supine	2.2±1.7	3±1.8	0.39
Upright	0.40±0.51	0.32±0.52	0.61
Out bed, min	0.28±0.58	0.21±0.16	0.61
Transitions, n			
Small	17.23±11.3	12.8±9.44	0.33
Medium	4.80±4.4	1.93±2	0.30
Large	2.15±2.17	1.62±1.9	0.09
Extra large	0.95±1.07	1.25±1.5	0.62
Sitting	8.64±8.30	6.68±2.10	0.32
Total transitions	34±18	24±13	0.03
Total Transition per hour	4.4±2.1	2.65±1.35	0.03

Note: † Data presented as geometric means and logSD.

5.5 Discussions

5.5.1 Significance of the findings

This chapter describes the baseline data for the group who had cough and sleep actigraphy monitoring as a sub-study of the O-COPD trial. Data showed a significant association found at the baseline between nighttime cough frequency and sleep disturbance indicated by actigraphy monitoring. We found cough at night correlated with the number of times the patient got out of bed and also the number of body position changes (transitions), suggesting that this may be a causal relationship. Correlation findings suggested that the LCQ, the primary endpoint, is correlated with 24h cough frequency, thus providing an objective foundation for this measurement. Nighttime cough frequency, particularly, is correlated with Cough-VAS, and fatigue score. The additional analysis that involved CAT items showed that increase in CAT items (cough and sputum) is significantly corelated with increase cough frequency. Finally an additional analysis that using the sputum frequency scale showed that sleep disturbance was significantly greater in COPD with DSP.

5.5.2 Cough frequency

The average 24h cough frequency in our study was 134 coughs (8.9 coughs per hour) which was the same average reported for stable COPD by Sumner et al (9 coughs per hour)(Sumner, Woodcock et al. 2013). In our study protocol we were not evaluate the impact of colour or volume of sputum production due to study protocol limitations related to the COVID-19 pandemic but, sputum frequency scale demonstrate that sputum clearance was important factor to alter cough frequency in general and cough pattern at night, most likely in COPD with daily sputum production. This would be in keeping with the report by Sumner et al when they found

that sputum clearance is an important predictor of cough frequency (Sumner, Woodcock et al. 2013).

5.5.3 Subjective cough measurements

Cough frequency was significantly associated with LCQ (r= -0.60) and Cough-VAS (r=0.49), which supports the validity of these subjective cough measurements in the clinical routine. This agrees with prior findings reported about the relationship between subjective and objective cough monitoring (Birring, Matos et al. 2006, Smith, Owen et al. 2006, Crooks, Hayman et al. 2016). It is likely that using both measurements to capture the burden of cough may offer a better understanding of the cough from different angles and help to provide a better treatment plan (Vertigan, Kapela et al. 2021). Also, objective cough assessment has the advantages of quantifying the cough frequency, describing the distribution of the cough during the daytime and night-time, and reflecting the actual cough frequency instead of describing a general perception.

5.5.4 Nighttime cough and sleep actigraphy

In COPD with mucus hypersecretion, nighttime disturbance by cough is an issue for patients. (Hartman, Prinzen et al. 2015, Spina, Spruit et al. 2017, Orme, Steiner et al. 2019). We assessed the association between nighttime coughs and sleep actigraphy using simultaneous data from two objective monitors. Nocturnal cough frequency and sputum clearance were significantly associated with actigraphically measured sleep disturbance. This is a possible sign that cough causes arousal from sleep and thus that can lead to poor and insufficient sleep in this population (Fischer, Gross et al. 2018) , and this may say something about the relationship between nocturnal cough frequency and daytime fatigue. Hartman et al. in a cross-sectional study with COPD patients with frequent sputum production found that recurrence of the sputum production

was significantly associated with poor sleep quality measured with Pittsburgh sleep quality index. Our findings were similar to earlier research findings on the relationship between sputum production and sleep disturbance, but this time the cough frequency was objectively linked to the sleep disturbance (Hartman, Prinzen et al. 2015). This phenomenon could be explained by sputum accumulation triggering cough episodes during night, which then cause sleep movements and getting out of bed, potentially contributing to poor sleep quality (Fischer, Gross et al. 2018). An alternative hypothesis is that the patients is woken by some other factor and takes the opportunity to cough when awake; in the future studies employing video polysomnography would be useful to try to address the causality issue.

5.5.5 Fatigue

In our study we noticed that the sleep profile for COPD patients with sputum production exhibits a high rate of body transitions which may disturb the sleep and result in lowering the sleeping time, reducing the sleep quality and, consequently, increase daily fatigue. In addition, there was a moderate relationship between nocturnal coughing and fatigue (r= -0.75). There is some correspondence between our findings and the findings presented in the previous study by Orme et al., which concluded that increase overnight body movements in COPD were associated with reduced daily activity and sleep duration (Orme, Steiner et al. 2019). These data suggest that insufficient sleep caused by nocturnal cough contributes, in addition to sleep fragmentation, to fatigue. Our findings are in agreement with those reported by Spina et al. who found that sleep disturbance (measured using actigraphy) was significantly associated with overall fatigue as measured objectively by daytime sleepiness and additional naps during the day (Spina, Spruit et

al. 2017). It is important to examine whether the current findings are repeatable, as other factors could have caused the sleep disturbance and fatigue.

Several lessons can be learnt from the current study. Those COPD patients with frequent sputum production seem to cough more during the day than at night. Nevertheless, coughing may vary from one individual to another (i.e., phenotypes of COPD). The availability of cross-sectional data about cough frequency and cough characteristics in COPD for comparison is limited. It may be helpful to combine subjective and objective cough measurements in order to gain a more concise and deeper understanding of the cough in COPD with mucus hypersecretion. We haven't yet reached the point where a monitor can measure coughing without human assistance (i.e., using machine learning models and artificial intelligence), though this would facilitate epidemiological studies. All available objective cough monitoring is semi-automated, and the human factor is critical for spotting and confirming cough events. Coughs overnight most likely cause sleep disturbance with respect to the sleep profile and other sleep problems.

5.5.6 Follow up data for this subsequent group

Chapter 6 (Next chapter) discusses the effect of interventions (OPEP therapy and routine care) for three months on objective cough monitoring and sleep actigraphy. This analysis may shed some light on the aetiological relationship between cough and sleep fragmentation.

5.6 Limitations

The sample size for this study was small, but it was adequate and powered. Only patients who met the first three categories in the sputum frequency scale were included. Thus, all COPD patients included in this study were suffering from cough and sputum production (indicated by

sum of ≥5 out of 10 in the first two items (cough and sputum) from CAT tool), we don't have data about the cough when it less severe (i.e., sum of <5 in cough and sputum items of the CAT tool). The development of objective cough monitoring must consider more health and digital innovations such as machine learning and artificial intelligence to reduce the time consumption needed for analysis and increase the accuracy of detecting the cough. Future research should examine factors such as muscle strength and expose to irritants in relation to cough frequency. Furthermore, it would be interesting to evaluate the impact of treatments on objective cough frequency, as this will be discussed in Chapter 6

5.7 Conclusion

COPD patients cough more during the day than at night. Coughing at night is associated with increased sleep disruption, as determined by sleep movements, and a higher daytime fatigue score. Combined subjective and objective monitoring of cough in COPD is feasible and can provide a better understanding of cough symptomatology.

6 Follow up data for the sub-study from the O-COPD trial: Objective cough monitoring and sleep actigraphy.

6.1 Abstract

Rationale: OPEP therapy can be added to routine care to optimise COPD management. Therefore, in this sub-study, we evaluated whether adding OPEP therapy to usual care for three months would reduce cough frequency and sleep actigraphy compared to UC.

Methods: This is a sub-study of the O-COPD trial (ISRCTN44651852), which randomised stable patients with COPD reporting a productive cough (daily or most days in the preceding month) and scoring ≥5 out of 10 in the first two items (cough and sputum) of the CAT score, to either usual care including the active cycle of breathing technique (ACBT) or to usual care with the addition of an Acapella device for three months. Cough frequency was recorded using the Leicester Cough Monitor (LCM), sleep parameters by actigraphy using the DynaPort MoveMonitor (McRoberts BV, The Hague, the Netherlands). Cough reported as 24-hour cough frequency. Differences between the groups were compared by linear mixed model using baseline values as covariates. Pearson correlation coefficients were used to analyse the association between continuous variables. P-value less than 0.05 consider statistically significant.

Results: Out of the 45 patients in the O-COPD trial (OPEP therapy n=25, usual care n=20) took part in this sub-study, 33 (OPEP n=18, usual care n=15) were completed the follow up measurements. 12 participants dropped out. Thus, we reported on patients with age 63±10 years, female (n=14), and ex-smokers (n=21). Three months use of OPEP therapy produced a statistically significant reduction in this sub-population in 24hr cough frequency compared to

usual care (geometric mean difference and [95% CI]; -60 coughs/24hrs, [-43 to -95]: p<0.001). The difference in daytime cough frequency was (geometric mean difference and [95% CI]; -16, [-8 to -63]; p= 0.012) and the night-time cough frequency was (-43, [-6.2 to -53]; p=0.014). The difference between groups in sleep disturbance was not statistically significant. After three months of OPEP therapy, there was a statistically significant association observed between change in 24hr cough frequency and change in LCQ (r=-44, p =0.04) and sputum frequency scale (r= 0.51, p= 0.006) and sleep actigraphy (getting out of bed, r= 0.49; times spent out of bed, r=0.38; and small transitions r= 0.38; p-value for all <0.05).

Conclusion: For people with COPD reporting frequency sputum production, use of an OPEP device reduces 24h cough frequency. The reduction in cough frequency was associated with reduction in actigraphically determined sleep disturbance and fatigue score.

6.2 Introduction

In the O-COPD trial (previous chapters 4 and 5), we showed that adding an OPEP therapy to usual care for three months improved cough-related quality of life. We also found (chapter 5) a significant correlation at baseline between of cough frequency with fatigue and sleep movement in COPD with frequent cough and sputum production.

The rationale behind this element of the study is that the current literature on measuring the effects of treatment on cough outcomes in COPD has several gaps. First, objective cough monitoring is rarely used as a clinical outcome measure of treatment in COPD population (Spinou and Birring 2014). Second, available studies used subjective cough assessment to report change, which cannot reflect the actual impact of the treatments on cough and sputum production (Berkhof, Doornewaard-ten Hertog et al. 2013, Garner, Shaipanich et al. 2020). Next, methods to quantify cough need experts and/or additional time to process cough monitoring. Furthermore, there is no data available about the effect of non-pharmacological treatments (such as OPEP devices) on cough outcomes. To this end, in this chapter I describe: (1) whether adding OPEP therapy to the usual care for three months improves ambulatory cough monitoring and actigraphically determined sleep disturbance compared to usual care; (2) the impact of long-term treatments (OPEP therapy and Usual care) on the cough frequency as well as on sleep actigraphy, and (3) investigating the relationship of change, induced by intervention, between subjective and objective cough measures.

6.3 Methods

This chapter describes three month follow up data for the sub study discussed in the chapter 5. The participants were a subset group from the O-COPD (OPEP device to improve cough and sputum). Full details about the methods were described in chapters 3, 4, and 5. The baseline measurements for participants were described in chapter 5.

6.3.1 Outcomes

6.3.1.1 Cough frequency

Between group change in objective 24h cough frequency from the baseline.

6.3.1.2 Sleep actigraphy and sleep disturbance

Between group change in sleep movement parameters (night's rest time, movements intensity and duration, times out of bed, body postures, and transitions) from the baseline.

6.4 Measurements

6.4.1 Data recording and procedures

All procedures prescribed at the baseline in chapter 5 were repeated after three months for the follow up.

6.4.2 Statistical analysis

Data analysis was performed using SPSS version 26.0 (IBM, SPSS, Illinois, USA) and Prism 9.2.0 (GraphPad Software Inc, California, USA). The baseline characteristics were expressed as mean and standard deviation, median and interquartile ranges, frequencies and proportions, as appropriate. The distribution of the data was checked by normality tests. Logarithmic transformation was used for skewed data (i.e. cough frequency) to normalise the distribution,

and the data were expressed as geometric means (GEM) and logarithmic standard deviation (LogSD) (Sumner, Woodcock et al. 2013). Normally distributed data, without logarithmic transformation were reported as mean and standard deviation (SD).

Between group differences were compared using linear mixed model with adjustment to the baseline values as a covariate. For the sub-study outcomes, complete case analyses without imputation of missing data are provided only.

Cough frequency improvement refers to a reduction in cough frequency after three months. The improvement rate of cough frequency after treatment was calculated based on the previous literature by the following formula *"Cough frequency before treatment – cough frequency after treatment/cough frequency before treatment * 100"* to investigate the differences in prognosis between the treatment arms and presented as a proportion (Fukuhara, Saito et al. 2020).

Pearson's correlation coefficient was used to assess the relationship between continuous variables Statistical significance was determined by a 2-tailed p-value of <0 .05.

6.5 Results

6.5.1 Patient's characteristics

Figure 6.1 shows flow chart for the sub-study participants. Out of those 45 patients, 33 (OPEP n=18, UC n=15) participants completed the follow up objective measurements. Twelve patients (27%) dropped out from the follow up. Three patients were not happy to have the LCM, while two patients were uncomfortable wearing the DynaPort.

Table 6.1 presents the characteristics of participants who completed the follow up time point. The UC group was younger than the OPEP group (62±10 years versus 65±9.8 years). Number of

females were similar (n=7) in both groups. There were no significant differences in the characteristics between the treatment groups.

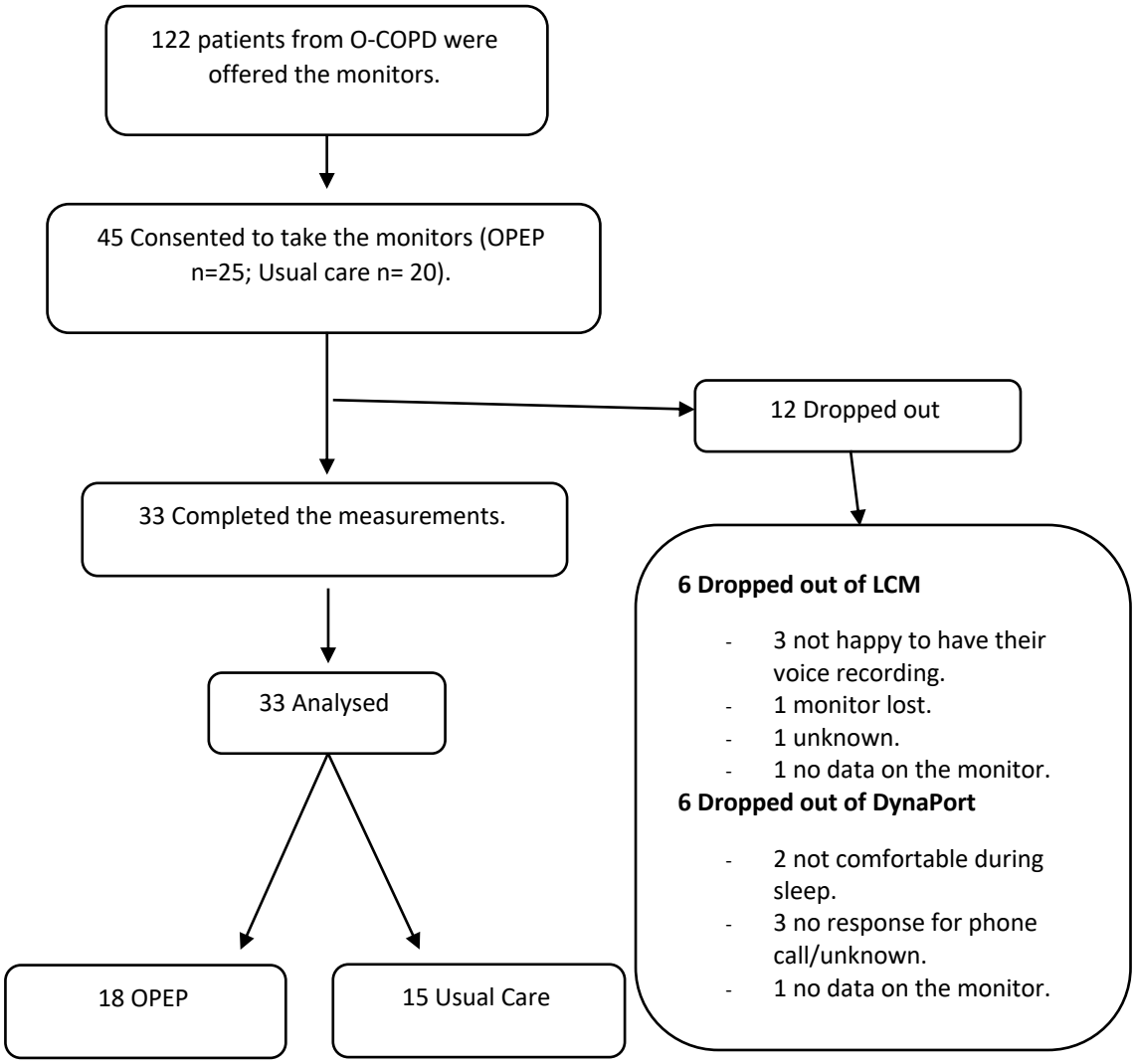


Figure 6.1 A flow chart for the participants.

Table 6.1 Characteristics for participants who completed the follow up time point (n=33).

Variable	Sample (33)	OPEP (n=18)	Usual care (n=15)	p-value
Age	63±10	65 ± 9.8	62±10	0.19
Gender (Female/male)	14/19	7/11	7/8	0.34
BMI	26.2±7.2	26.7±6.3	25.7±8.2	0.68
Smoking (Ex/smoker)	21/6	16/2	11/4	0.15
Packs per years[§]	16[12 to 26]	15 [12 to30]	20 [12 to 20]	0.26
Diagnosis (COPD II/III/IV)	9/21/11	0/13/5	2/8/5	0.18
AECOPD last year (1/2/3/>3)	10/5/5/6	5/4/2/2	5/1/3/4	0.24
LCQ	13.04±4.02	13.01±4.55	12.57±3.53	0.73
Cough-VAS, mm	50.57±26	49±25	52±28	0.74
Sputum scale	1.87±0.92	2.09±0.92	1.59±0.87	0.09

Note: Data presented as mean±SD or frequency and percentages. AECOPD: Acute exacerbation of COPD; [§] Mann-Whitney test. Higher score in LCQ, Sputum scale representing better outcome. Lower score in Cough-VAS representing better outcome.

6.5.2 Between group differences in cough

Table 6.2 and Figure 6.2 show between-group differences in 24h cough frequency (Day and Night). Three months use of an OPEP device was produced a statistically significant reduction in 24h cough frequency compared to usual care (total coughs; p <0.001, daytime coughs; p =0.012, and night-time coughs; p =0.014).

Table 6.2 Summary of cough difference between groups before and after treatment.

	OPEP			UC			Between group difference	p-value
Cough parameters	Pre (n=25)	Post (n=18)	GEM Change	Pre (n=20)	Post (n=15)	GEM Change		
24-h cough frequency, n	153±0.32	63±0.39	-90±0.33	107±0.39	77±0.38	-30±0.39	-60 (-43 to -95)	<0.001
Daytime coughs, n	97±0.33	54±0.36	-43±0.39	71±0.42	44±0.41	-27±0.42	-16 (-8 to -63)	0.012
Daytime coughs per hour	6.36±0.27	3.25±0.43	-3.34±0.80	4.20±0.45	2.60±0.38	-1.59±0.73	-1.75[-4.39 to 0.88]	0.18
Nighttime coughs, n	75±0.43	27±0.80	-45±0.43	38±0.44	33±0.51	-5±0.43	-43 (-6.2 to -53)	0.014
Nighttime coughs per hour	8.75±0.51	2.60±0.71	-5.77±2.39	5.74±0.48	5.07±0.48	-1.00 ±2.00	-4.77[-10.49 to 0.95]	0.09

Note: GEM Change; geometric mean change; LogSD: log standard deviation; UC: Usual Care; CI: confidence intervals; MD: Mean difference adjusted for the baseline values. Data presented as geometric means and Log (SD).

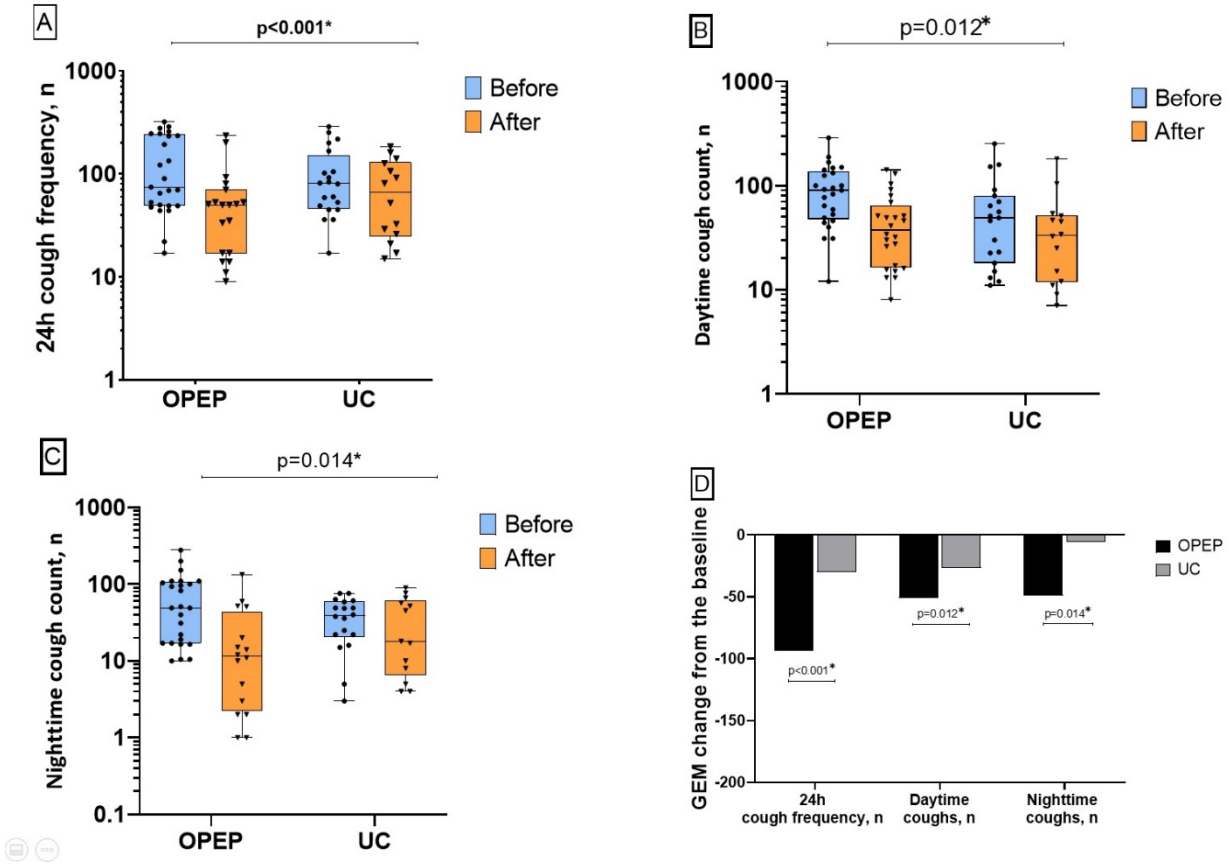


Figure 6.2. Comparison of 24-h cough frequency before and after treatments (OPEP and Usual care (UC)). (A) comparison of 24-h cough frequency, (B) comparison of Daytime cough frequency, (C) comparison of the night-time cough frequency, and (D) Between group geometric mean change in 24-h cough frequency, daytime cough frequency, and nighttime cough frequency.

6.5.3 Correlation of improvement rates in cough frequency before and after the treatment.

I also reported the correlation between improvement rates in both treatment arm. Overall, there was a significant correlation between improvement in 24h cough frequency and nigh-time cough frequency, but not daytime cough frequency (r= 0.44, p= 0.021; r= 0.22, p=0.25). This reduction in night-time cough frequency was observed in the OPEP group (r= 0.54, p = 0.022), but not to the usual care (r= 0.41, p = 0.13).

6.5.4 Between groups analysis in sleep actigraphy

Table 6.3 shows between group differences for sleep actigraphy. There were no statistically significant differences between study arms in sleep movement parameters.

Table 6.3. Between group changes in sleep movement parameters.

	OPEP (n=18)	UC (n=15)	Between groups	
Parameters	**Change**	**Change**	**MD (95CI%)**	**p-value**
Duration night's rest, hour	-0.21 ± 2.44	0.93 ±2.95	-1.15 (-3.72, 1.80)	0.16
Lying down, hour	0.22 ±4.06	-0.07 ±3.3	0.30 (-2.69,4.04)	0.68
Total Movement duration, min	0.21 ±5.41	-0.39 ±2.01	0.61 (-4.54,7.66)	0.93
Getting out of bed, n	-0.60 ±1.80	0.12 ±1.64	-0.73 (-1.50,0.04)	0.06
Body postures, min				
Left	0.64±2.46	0.21 ±1.66	0.43 (-1.26,2.83)	0.12
Right	-0.03 ±2.02	-0.19 ±2.10	0.16 (-1.47,2.32)	0.40
Supine	-0.49 ±1.88	0.08 ±1.82	-0.58 (-1.89,1.54)	0.38
Upright	-0.10 ±0.70	0.01 ±0.45	-0.11 (-0.83,0.32)	0.86
Out bed, min	-0.06 ±0.42	0.08 ±0.54	-0.15 (-0.80,0.08)	0.23
Transitions, n				
Small	0.69±8.43	0.75 ±4.93	-0.05 (-9.89,9.85)	0.98
Medium	0.00±3.11	-0.17 ±5.12	0.17(-4.18,5.27)	0.86
Large	-0.07 ±1.95	-0.22 ±1.63	0.15 (-0.86,2.56)	0.73
Extra large	-0.23 ±1.10	0.02 ±0.32	-0.25 (-0.65,0.13)	0.19
Sitting	0.41±6.32	0.65 ±4.81	-0.23 (-3.32,2.80)	0.78
Total transitions	0.64±17.63	0.47 ±9.01	0.16 (-8.39,8.72)	0.96

Note: n: frequency; g: grams; min: minutes; MD: mean difference from linear mixed model adjusted for baseline.

6.5.5 Correlation of change in cough frequency and measurements.

Table 6.4 shows the correlation of change in cough frequency and other measures. The change in mean expressed as **Δ** symbol. Using Pearson correlation analysis, it was determined that Δ in daytime cough frequency is significantly correlated with not only Δ LCQ (r= 0.44, p =0.048) but also, Δ Cough-VAS (r=0.51, p=0.005) and Δ sputum scale r= 0.51, p= 0.006). the Δ in night-time cough frequency is significantly correlated with Δ in getting out of bed (r=0.49), Δ in time out of bed (r=0.38), Δ small transitions (r=0.38), Δ in sitting transitions (r=0.34), and Δ in total transitions (r=0.35).

Table 6.4 Correlation of change of cough frequency and other study measures after three months.

Measurements	Direction of change	Correlation coefficient	p-value
Δ LCQ	(+)	0.44	0.048[a]
Δ LCQ psychological	(+)	0.42	0.033[a]
Δ Cough-VAS	(-)	0.51	0.005[a]
Δ Sputum scale	(+)	0.51	0.006[a]
	(+)	0.42	0.028[b]
Δ Getting out of bed, n	(-)	0.49	0.009[b]
Δ Time out of bed, mins	(-)	0.38	0.046[b]
Δ Small transitions, n	(+)	0.38	0.040[b]
Δ Sitting transition, n	(-)	0.34	0.049[b]
Δ Total transitions, n	(-)	0.35	0.061[b]

Note: Δ: change from the baseline; (+): increase; (-) decrease; n: frequency; g: gram; mins: minutes. Increase in LCQ, FACIT, and sputum scale are representing better outcome. Decrease in cough- VAS is representing better outcome. a, the daytime cough frequency; b, the nighttime cough frequency.

6.6 Discussions

6.6.1 Significance of the findings

In this subset analysis OPEP reduced 24-h cough count suggesting that it is representative of the bigger cohort, with corresponding. In addition, the improvements in cough frequency after treatment -OPEP device and UC - is consistent with LCQ questionnaire. Most importantly, the

reduction in cough frequency after treatment were significant at night-time compared to the daytime cough favouring the OPEP treatment. Adding the OPEP device to usual care did not have a statistically significant impact on sleep movement parameters however, although there was a correlation between reduction in night-time cough frequency and reduction in sleep disturbance after three months.

6.6.2 OPEP Therapy for cough and sputum production.

These results demonstrate that adding OPEP therapy to usual care is an effective way to assist patients in airway clearance while also helping them manage their cough, compared to the usual care alone. There was an observation that the reduction in couch frequency was occur in both treatment groups. Perhaps this was due to the experience that the patients were able to perform the therapies independently. Another possibility is that the study actually happened during the COVID-19 outbreak, when individuals with COPD were encouraged to stay at home and follow their regular care regimen, which included medications and breathing exercises (Kaye, Theye et al. 2020, Philip, Lonergan et al. 2020). It could be also due to the behavioural changes or increased anxiety associated with the pandemic, as people are fearful of being infected with COVID-19 and/or not being able to cope with the symptoms (Philip, Lonergan et al. 2020). All have contributed to enhance the effectiveness of treatments in reducing cough frequency to some extent, but the reduction in cough frequency was three times greater in the OPEP group when compared to the usual care.

It should be noted that coughing and sputum production are complex processes, and they may change over time as a result of natural recovery processes (i.e., recovery from exacerbations) (Lee, Matos et al. 2013, Crooks, Hayman et al. 2016). For this reason, a recent cough experts

panel reported that there is insufficient evidence to recommend pharmacological or non-pharmacological treatments as routine to manage or reduce cough in COPD (Malesker, Callahan-Lyon et al. 2020). OPEP treatment can be added to the routine care as a solution to improve sputum expectoration and, as a result, managed the ongoing cough. Our findings, possibly support the idea that adding OPEP treatment to the usual care offers optimisation to the usual care in order to manage sputum and cough in COPD. Similar idea have been previously reported in very small study by Christines et al. (Christensen, Nedergaard et al. 1990). The study evaluates the long-term effect of 12- months treatment of Positive expiratory pressure mask (PEP mask) on the acute exacerbation events in COPD, compared to the usual care. The study reported that the difference in cough and sputum expectoration between the PEP group and usual care was statistically significant, favouring the PEP treatment. However, the actual data for cough and sputum production were not reported by the authors (Christensen, Nedergaard et al. 1990). There were inconsistencies in measuring or reporting cough outcome in COPD population, as well as we lack knowledge about the impact of either pharmacological or non-pharmacological treatments on objective cough monitoring in COPD.

6.6.3 Improvements in cough frequency in COPD

In contrast to COPD population, few studies investigating the impact of treatments on 24-cough frequency in chronic respiratory diseases such as patient with refractory chronic cough(Ryan, Birring et al. 2012), adult with cystic fibrosis (Smith, Owen et al. 2006) , asthma (Fukuhara, Saito et al. 2020), pulmonary tuberculosis (Proaño, Bravard et al. 2017) or bronchiectasis(Patterson, Hewitt et al. 2007). However, all treatments were pharmacotherapies. Gabapentin reduces cough frequency by 51% in refractory chronic cough patients as compared to a placebo (lactose

tables)(Ryan, Birring et al. 2012). Standard therapy with intravenous antibiotics is responsible with 51% reduction in daytime cough frequency and 72% reduction in night-time cough frequency in adults with cystic fibrosis.(Smith, Owen et al. 2006). Appropriate treatment with inhaled corticosteroids, either alone or in combination with long-acting agonists, reduces cough frequency by 83% in asthmatic patients (Fukuhara, Saito et al. 2020). In the case of pulmonary tuberculosis, 14 days of appropriate treatment (not described) results in 79% reduction in 24-hour cough frequency (Proaño, Bravard et al. 2017). Only one cross-over trial compared the effectiveness of Acapella treatment versus Active Cycle of Breathing in individuals with Bronchiectasis. The study found no statistically significant difference in cough frequency between treatments (data not reported and cough manually counting by the physiotherapist)(Patterson, Hewitt et al. 2007). It is true that cough patterns differ from one chronic disease to another, but it appears that the treatments described above are more related to chronic cough rather than acute cough. To date, little is known about cough frequency and pattern or the effect of different treatments on modifying cough in COPD patients. Nonetheless, we showed that OPEP therapy was responsible for 58% reduction in 24-hour cough frequency.

6.6.4 Improvements in nighttime symptoms and sleep movements

Our data showed that improvement in objective cough frequency after OPEP treatment was associated with improvement not only in cough-related quality of life, cough severity, sputum expectoration, and fatigue score, but also in sleep movements. It is important to note, however, that the questionnaires do not pertain specifically to COPD, and any assessment is dependent on the perception of the patient. Therefore, actigraphy offered a novel line of support for the effectiveness of OPEP therapy reducing night-time symptoms in COPD. Our study is currently the

first to show that the decrease in cough frequency after OPEP treatment is most likely to occur at night. The possible explanation for this could be related to the mechanism of airway clearance. Airway clearance techniques (including OPEP treatment) are generally performed during the day rather than at night. This results in more sputum expectoration as well as preventing the accumulation by excessive sputum that might cause nighttime wakefulness. In our study, we have these ideas supported by the results in the OPEP group where it shows greater improvement at night-time cough compared to the day. Another explanation for this mechanism is the results of Pearson correlation between night-time cough and sleep movements. Our analysis revealed that the sleep movements were modified after treatments. As an example, when nocturnal cough frequency was reduced, the sitting position also reduced ($r=0.33$, $p=0.045$), whereas the supine position increased ($r=0.38$, $p=0.024$). A reduction in productive cough during the night may be linked to effective airway clearance via OPEP during the day. This explanation is supported by data from a Pan-European study that shows that cough and sputum are the most troublesome symptoms causing waking up (Kessler, Partridge et al. 2011).

6.6.5 Clinical implications

Considering current knowledge gap and our own findings, we learned several lessons from the current study. First, adding OPEP to usual care is beneficial to reduce cough frequency at night, and sleep disturbance. Additionally, monitoring cough frequency as well as sleep movements provide better understating to the assessment of the treatment impact in people with COPD.

Second, there are two available interventions for managing cough and sputum production, either pharmacological or non-pharmacological. So far, we know that pharmacological treatments (i.e., antibiotics, mucolytics, bronchodilators) are reviewed and commonly prescribed (as prophylactic

or routine treatment) for COPD with frequent sputum production, but little is known about their safety and mechanism in managing night-time symptoms (Berkhof, Doornewaard-ten Hertog et al. 2013, Barker, Laverty et al. 2017, Herath, Normansell et al. 2018). Medicines, in combinations, perhaps substantially improve mucociliary clearance either by attacking the inflammatory markers or viscosity properties of the mucus (Smith and Woodcock 2006) while the OPEP therapy augment sputum clearance and natural cough mechanism by losening the mucus, and facilitating mucus mobilisation (Alghamdi, Barker et al. 2020).

Third, in routine COPD care, night-time symptom management is important to keep the disease under control and prevent overall fatigue. The management of COPD should consider night-time symptoms, specifically, cough and sputum production. Our findings possibly justify the association between frequent sputum production and sleep movements that has been defined in the previous research (Hartman, Prinzen et al. 2015) and also demonstrated that productive cough in COPD is a potential disturbance during sleep, with respect to other factors contributing to that matter. Thus, using OPEP therapy is a possible and simple solution to enhance sufficient sleep, less disturbing, and minimize fatigue in COPD patients with frequent productive cough.

Fourth, since OPEP therapy can provide additional dynamic assistance to usual airway clearance therapy such as ACBT and potentially reduce overnight cough-related wakefulness. However, the OPEP family has several devices which provide the same function as the Acapella. In chapter 3, using a systematic review and meta-analysis methodology, I was able to link the benefits of using different OPEP devices to better outcomes in COPD, particularly the overall health status (including cough and sputum expectoration), health-related quality of life, exacerbations, and exercise capacity (Alghamdi, Barker et al. 2020). However, I observed that none of the included

studies evaluated the benefits of OPEP devices on night-time symptoms, including cough and sputum production or sleep movements. This is not surprising as the night-time symptoms in COPD receive less research attention (Agusti, Hedner et al. 2011). Large and longer clinical trials are needed to evaluate the impact of OPEP devices on improving COPD symptoms including cough and sputum production.

Finally, I have reported the cough frequency and the sleep movements for COPD people who were classified as frequent cough and sputum producers based on the first three categories in the sputum scale (described in chapter 5). However, the current data should be interpreted with caution as a large proportion of COPD subjects who were classified with less frequent cough and sputum production (category 4 and category 5 in the sputum scale) were not included in the analysis.

6.6.6 Limitations and future directions

Despite the limitations mentioned in the main trial (the O-COPD trial), future research should pay attention to important observations from the current study. First, participants who received OPEP therapy were already on standard care (NICE recommendations 1.2.40 and 1.2.99: including oral mucolytics and ACBT), this to some extent, had an interaction effect with the OPEP therapy as there was no supporting evidence of direct comparison of OPEP theory to medications or usual care in COPD. Second, even the spectrum of COPD with productive cough includes different disease phenotypes. This may introduce interpretation bias for the cough pattern as the acute cough is different than chronic cough. This aspect regarding the cough pattern still lacking and there were not enough data from large and longitudinal studies. It has been reported that the cough frequency longitudinally falls post-8-weeks of COPD exacerbations (Crooks, Hayman

et al. 2016). I was not able to evaluate the impact of OPEP therapy on stable COPD at 6-weeks in the current study as the protocol time points were at the baseline and three months. However, we scheduled the 6-weeks phone call to remind participants about using the treatments (Acapella or UC) and keep the diary cards up to date. Finally, the night's rest movements due to nocturnal cough in people with COPD must repeated using more sophisticated minute by minute analysis, ideally with video polysomnography, to explore if nocturnal cough event is simultaneous with overnight sleep movements (overnight polysomnography or video recording) or investigate if body positioning during sleep is influence or influenced by cough event. Future research also must consider improving sleep quality and reducing night-time symptoms as the recent systematic review reported that sleep quality in COPD is a predictor of mortality (Lewthwaite, Effing et al. 2017).

6.7 Conclusion

Compared to usual care, OPEP therapy was found useful in reducing objective cough frequency and improving cough-related quality of life in three months in people with COPD. This clinical evidence will help to fill the gap of knowledge in measuring the impact of OPEP therapy on cough outcomes. The improvements seem to apply more in night-time than daytime. Further research is needed in this area to elucidate the impact of non-pharmacological therapy on cough outcomes.

7 Discussion and future work

7.1 Summary of thesis aims

In this thesis, I had four main objectives which are summarised as follows:

- The first objective was to use systematic review methodology to rigorously examine the current evidence on the use of OPEP therapy for cough and sputum clearance in patients with COPD who frequently produce sputum.
- The second objective was to conduct a randomised clinical trial (acronym: O-COPD) to evaluate the impact of OPEP therapy on the health-related quality of life over three-months in COPD who frequently produce sputum.
- The third objective was to assess the correlation of objective cough count, sleep disturbance, and fatigue in people with COPD who frequently produce sputum.
- The final objective was to evaluate the impact of OPEP therapy on cough frequency and sleep disturbance in a subset of the O-COPD group.

7.2 Summary of the main findings in the thesis chapters

1. **Use of oscillatory positive expiratory pressure devices to augment sputum clearance in COPD: a systematic review and meta-analysis (Chapter 3)**

- OPEP devices generally provides intrathoracic oscillations via positive expiratory pressure and stent the airway during the expiration using theses oscillations. This can loosen mucus and generate effective cough for COPD patients with frequent sputum production.

- OPEP therapy can reduce COPD symptoms (cough and sputum), exacerbations, and improve exercise capacity.
- The meta-analysis has shown that OPEP devices in stable COPD improve quality of life, sputum clearance, exercise capacity, and reduce exacerbations, as well as antibiotic use.
- OPEP therapy in AECOPD reduce hospital length of stay.
- The observed effects of OPEP therapy were generally modest, and the findings were based on a limited number of studies with considerable variation in risk of bias and most trials were short-term.

2. Oscillatory positive expiratory positive (OPEP) Therapy in COPD: The O-COPD Randomised Clinical Trial (Chapter 4)

- The O-COPD demonstrated that the long-term regular use of OPEP therapy can advocate similar impact as the pharmacological therapy to improve cough-related quality of life.
- The O-COPD trial showed that adding OPEP therapy to usual care for three months can significantly improve general (EQ5D) and specific -related quality of life (LCQ), fatigue, and the sputum frequency scale.
- The psychological domain of LCQ was most sensitive to change.
- In the context of COPD, the effect observed was generally modest with people whom sputum production is major concern.
- The number of COPD exacerbations decreased significantly at the 6-week phone call in the OPEP group.
- At baseline, LCQ was correlated with general quality of life (EQ5D), symptoms in COPD patients (CAT), fatigue score (FACIT) and sputum frequency scale.

- After three months, LCQ changes were significantly related to FACIT, EQ5D, sputum frequency scale, Cough-VAS, and CAT score.
- The O-COPD trial protocol provides a framework that can be used to evaluate other OPEP devices/other outcomes in this group of patients.
- The approach of remote monitoring for OPEP therapy is feasible and practical.

3. Relationship between objective cough monitoring and actigraphy sleep movements: Baseline data from the O-COPD clinical trial (Chapter 5)

- 24-hour cough frequency is correlated with LCQ total score and subjective measurements.
- Nighttime cough count is correlated with cough-VAS and fatigue score.
- At baseline, cough counts were correlated with measures of sleep disturbance and fatigue.

4. Follow up data for the sub-study from the O-COPD Trial: Objective cough monitoring and sleep actigraphy (Chapter 6).

- Available post-treatment data demonstrated that OPEP treatment was associated with a reduction in cough frequency, compared to usual care.
- Sleep actigraphy measures of sleep disturbance did not differ between study arms.

7.3 Discussion

In light of the findings of this PhD work, the O-COPD trial showed improvements in cough-related quality of life (LCQ) in OPEP therapy group compared to usual care. This was accompanied by improvement in FACIT score, EQ5D, sputum clearance scale and a reduction in acute

exacerbations reported. A reduction in cough counts in the treatment arm was confirmed by objective monitoring in a subgroup, supporting the symptom benefit reported.

My PhD dissertation started with reviewing the current evidence which allowed me to explore the knowledge and research gaps related to the OPEP therapy. Lack of evidence, as well as the absence of clinical consensus regarding the effectiveness of sputum clearance techniques in guidelines, has meant that their use is much less common than the prescription of mucolytic drugs (Barker, Laverty et al. 2017, Alghamdi, Barker et al. 2020). Our group previously explored respiratory physiotherapist attitudes regarding the use of OPEP devices in COPD. According to respiratory physiotherapies, OPEP device would be considered for individuals with daily, difficult to clear thick sputum, but not for those who do not produced sputum daily (Barker, Laverty et al. 2017, Alghamdi, Barker et al. 2020). My findings from the O-COPD trial imply that OPEP devices can help a wider range of COPD patients than just those with the worst sputum burden. The simple criteria for patient selection of OPEP therapy are mostly relevant to the clinical practice as I used the sum of ≥5 out of 10 in the CAT cough and sputum items from the CAT assessment tool. CAT is being simply and widely used in the clinic to screen the symptoms before routine check or prescribing an intervention (Price, West et al. 2014, Karloh, Mayer et al. 2016).

My data showed that between group difference in LCQ and FACIT were matching with the published MCIDs of LCQ = 1.3 unit and MCID of FACIT = 2.8 unit (Berkhof, Doornewaard-ten Hertog et al. 2013, Nordin, Taft et al. 2016). ACBTs were taught to patients in the usual care arm, and they were encouraged to use them three times daily. This resulted in better sputum clearance than would normally occur. This would tend to underestimate the treatment effect of

the device. Importantly, the Acapella device also produced a substantial reduction in objective cough frequency compared to ACBT alone.

In COPD with mucus hypersecretion, nocturnal cough counts were partly related to sleep disturbance and getting out of bed at the baseline. This phenomenon was reported in previous studies (Hartman, Prinzen et al. 2015, Spina, Spruit et al. 2017, Orme, Steiner et al. 2019). The uniqueness about our findings is that we assessed the correlation between nighttime cough counts and sleep actigraphy using paired data from two objective monitors. Nighttime cough count and sputum clearance at baseline was significantly associated with sleep actigraphy as well as sleep item on the CAT questionnaire. In this population, cough may be a sleep arousal, which can lead to insufficient and poor sleep (Fischer, Gross et al. 2018) , and this may say something about the relationship between nocturnal cough count and poor sleep quality or daytime fatigue. earlier research findings on the relationship between sputum production and sleep disturbance justify this (Hartman, Prinzen et al. 2015), but for the first time the cough frequency was objectively linked to the sleep disturbance. However, between group difference in sleep actigraphy was not statistically significant in both study arms.

7.4 Limitations of the studies

In this meta-analysis, single-session studies were excluded, and only studies that evaluated the short-and long-term impact of OPEP devices on key outcomes were included. It is hard to evaluate the acute impact of a single-session OPEP device on a prolonged outcome such as quality of life. Moreover, different study designs (e.g. RCTs and RXTs) with different quality levels

were considered in the meta-analysis. However, due to incomplete data, it was challenging to pool the results for some other outcomes such as cough frequency.

In the O-COPD trial, there were some limitations which must be acknowledged. First, the duration of the study was not long enough to detect if OPEP therapy for longer period of time (i.e., 6 months, 12 months) would provide significant impact on treatment cost or other patient outcomes such as time of first COPD exacerbation. The COVID-19 pandemic has made video conferencing and video links a viable option for training on acapella instead of face-to-face training. This has no impact on the treatment process and has shown that remote treatment via telehealth can benefit some patients. Six weeks phone call have demonstrated that all participants watched the video link at least once before doing Acapella treatment or ACBT.

Also, the COVID-19 outbreak shifted the study from a multicentre to be a single centre, and this reduced the opportunity to explore the impact of OPEP device in different geographical locations with different COPD population. In the O-COPD trial, there was no placebo or shame device as these comparators may have impact on sputum clearance. The usual care group received ACBT exercises and were encouraged to preform it three times a day, which is not usually performed by patient in routine care.

In the sub-study, the sample size for this sub-study was small, but it was adequate and powered. Only patients who met the first three categories in the sputum frequency scale were included. All COPD patients included in the study were suffering from cough and sputum production (indicated by sum of ≥5 out of 10 in the first two items (cough and sputum) from CAT tool), yet

we don't have data about the cough when it less severe (i.e., sum of <5 in cough and sputum items of the CAT tool).

7.5 Future work

It is possible that OPEP devices work with certain groups but not with others, so it would be interesting to evaluate that in different COPD phenotypes or different levels of airflow obstruction. Future studies need to evaluate the impact of OPEP therapy within different types of study designs (e.g., daily episodic or prophylactic use) and consider different stratification on entry (e.g., on radiological appearance, CAT score combinations, or on the airway microbiome) as well as reporting the outcome of interest using gold-standard measures such as video polysomnography.

In the context of future clinical trials of OPEP therapy, it could be of interest to investigate the differences and similarities between OPEP devices using direct comparison of two devices in the COPD population (i.e., Acapella versus Aerobika). Adding to that there is a call for long term clinical trials with a bigger sample size to evaluate the impact of OPEP devices on the recurrent COPD exacerbations and/or health economics.

The development of objective cough monitoring must consider more health and digital innovations such as machine learning and artificial intelligence to reduce the time consumption needed for and increase the accuracy of detecting the cough. Future research should examine factors such as muscle strength and how exposure to irritants affects cough frequency.

Finally, the night's rest movements due to nocturnal cough in people with COPD must be repeated using more sophisticated minute-by-minute analysis, to explore if nocturnal cough

events are consistent with overnight sleep movements (overnight polysomnography or video recording) or investigate if body positioning during sleep influences or is influenced by cough event.

7.6 Conclusion

The findings of this thesis suggest that adding an OPEP device is beneficial for people with COPD and regular sputum production. OPEP therapy is effective in improving general and specific health related quality of life, fatigue, and objective cough monitoring. Further research is needed with large sample size to evaluate longer term clinical and health economic outcomes.

Appendix 1. Ethical approval letter

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Nicholas Hopkinson
Respiratory Muscle Lab
Royal Brompton Hospital
Fulham Rd
SW3 6NP

Email: hra.approval@nhs.net

08 January 2020

Dear Dr Hopkinson

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

Study title:	**The O-COPD trial: Oscillatory Positive Expiratory Pressure (OPEP) devices to improve outcome in patients with Chronic Obstructive Pulmonary Disease (COPD)**
IRAS project ID:	**269494**
Protocol number:	**19IC5363**
REC reference:	**19/LO/1427**
Sponsor	**Imperial College London**

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

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

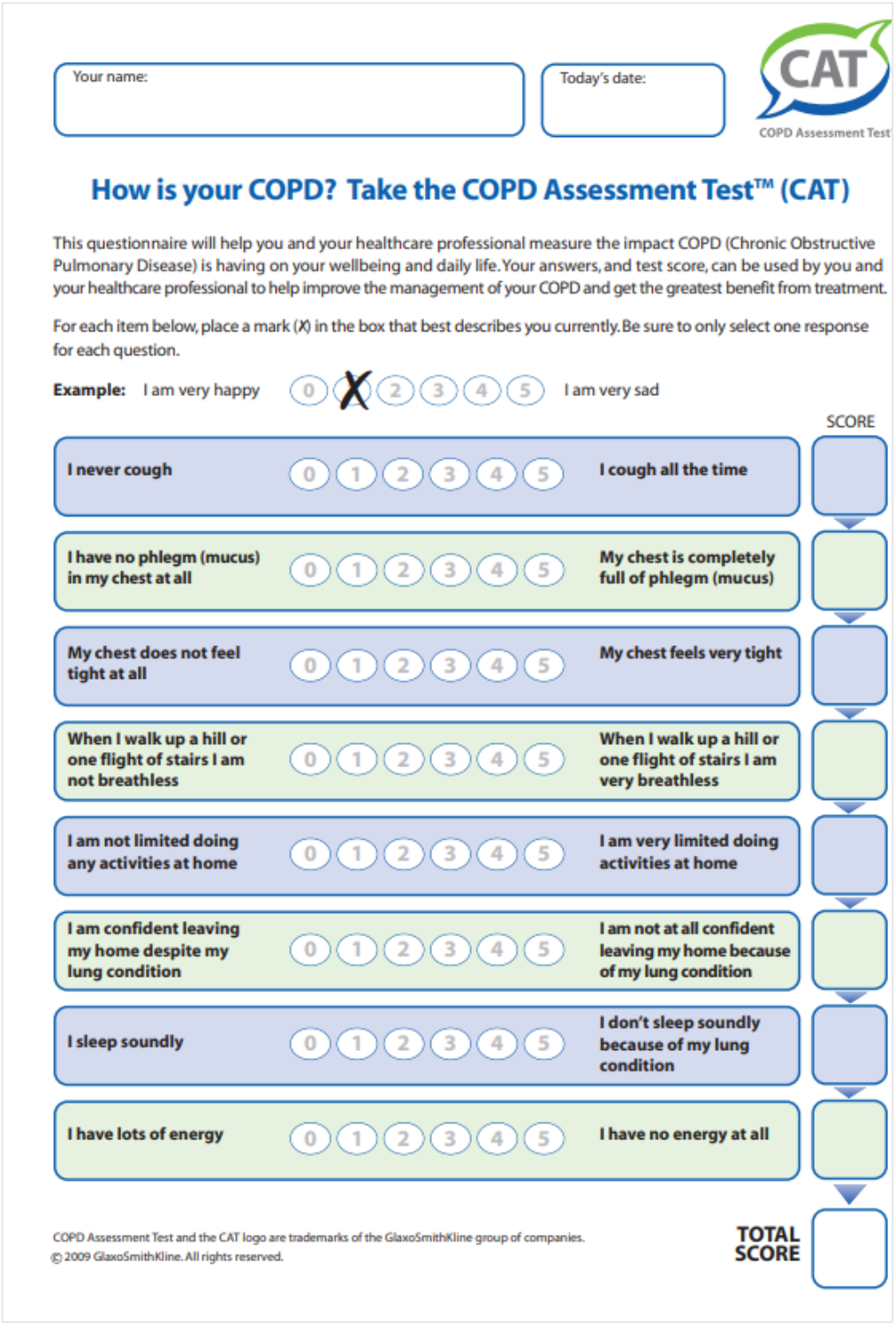
How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

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

Appendix 2. Sputum frequency scale

Grade	**How often do you cough up sputum**
1	Every day
2	Several days a week
3	Almost every day in the last month
4	On a few days in the last month
5	Only with lung or respiratory infections

Appendix 3. CAT score questionnaire



Your name:

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	
		TOTAL SCORE	

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Appendix 4. Search strategies of specific database

Ovid MEDLINE (1946 to March 2020)

1. Pulmonary Disease, Chronic Obstructive/ or Lung diseases, obstructive/ or Obstructive airway disease/ or Chronic obstructive lung disease/
2. Emphysema/ or Pulmonary Emphysema/ or Bronchitis, Chronic/ or Bronchitis/
3. Chronic Obstructive Pulmonary* Disease*.mp.
4. Chronic Obstructive lung* disease*.mp.
5. (COPD or COAD or chronic bronchi* or emphysema* or hyperlucent lung*).mp.
6. or/1-5
7. airway* clearance device*.mp.
8. airway* clearance therapy.mp.
9. sputum* clearance technique*.mp.
10. chest clearance*.mp.
11. Acapella*.mp.
12. Aerobika*.mp.
13. lung flute*.mp.
14. positive* expiratory pressure*.mp.
15. positive expiratory pressure therapy*.mp.
16. Oscillatory Positive Expiratory Pressure*.mp.
17. OPEP*.mp.
18. or/7-17
19. 6 and 18
20. limit 19 to (english language and humans)

EMBASE (1947 to March 2020)

1. Pulmonary Disease, Chronic Obstructive/ or Lung diseases, obstructive/ or Obstructive airway disease/ or Chronic obstructive lung disease/
2. Emphysema/ or Pulmonary Emphysema/ or Bronchitis, Chronic/ or Bronchitis/
3. Chronic Obstructive Pulmonary* Disease*.mp.
4. Chronic Obstructive lung* disease*.mp.
5. (COPD or COAD or chronic bronchi* or emphysema* or hyperlucent lung*).mp.
6. or/1-5
7. airway* clearance device*.mp.
8. airway* clearance therapy.mp.
9. sputum* clearance technique*.mp.
10. chest clearance*.mp.
11. Acapella*.mp.
12. Aerobika*.mp.
13. lung flute*.mp.
14. positive* expiratory pressure*.mp.
15. positive expiratory pressure therapy*.mp.
16. Oscillatory Positive Expiratory Pressure*.mp.
17. OPEP*.mp.
18. or/7-17
19. 6 and 18
20. limit 19 to (english language and humans)

CINAHL (EBSCO) (1960 to March 2020)

1. (MM “Lung Diseases, Obstructive”) OR (MM “Pulmonary Disease, Chronic Obstructive”)
2. (MM “Emphysema”) OR (MM “Bronchitis, Chronic”) OR (MM “Bronchitis”)
3. S1 OR S2
4. (TX “OPEP*”) OR (MM” Oscillatory Positive Expiratory Pressure”)
5. (MM” positive expiratory pressure therapy”) OR (MM” positive expiratory pressure”)
6. (TX” lung flute”) OR (MM” lung flute”)
7. (TX” Flutter device”) OR (MM” Flutter device”)
8. (MM” Aerobika”) OR (MM” Acapella”)
9. (TX” chest clearance technique*”) OR (TX” sputum clearance technique*”)
10. (TX” airway clearance therapy”) OR (MM” airway clearance device”)
11. S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10
12. S3 AND S11
13. Limit S12 to Language: English

Cochrane Database of Systematic Reviews – up to March 2020

ID	Search
#1	(airway clearance device):ti,ab,kw (Word variations have been searched)
#2	airway clearance technique
#3	airway clearance therapy
#4	chest clearance technique
#5	sputum clearance technique
#6	Acapella
#7	Aerobika
#8	Flutter device
#9	lung flute
#10	positive expiratory pressure
#11	positive expiratory pressure therapy
#12	Oscillatory Positive Expiratory Pressure
#13	OPEP
#14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#15	Chronic Obstructive Pulmonary Disease

#16 Chronic Obstructive lung disease

#17 COPD

#18 #15 or #16 or #17

#19 #14 and #18

PubMed – up to March 2020

1. airway[All Fields] AND clearance[All Fields] AND ("equipment and supplies"[MeSH Terms] OR ("equipment"[All Fields] AND "supplies"[All Fields]) OR "equipment and supplies"[All Fields] OR "device"[All Fields])
2. airway[All Fields] AND clearance[All Fields] AND technique[All Fields]
3. airway[All Fields] AND clearance[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])
4. ("thorax"[MeSH Terms] OR "thorax"[All Fields] OR "chest"[All Fields]) AND clearance[All Fields] AND technique[All Fields]
5. ("sputum"[MeSH Terms] OR "sputum"[All Fields]) AND clearance[All Fields] AND technique[All Fields]
6. Acapella[All Fields]
7. Aerobika[All Fields]
8. Flutter[All Fields] AND ("equipment and supplies"[MeSH Terms] OR ("equipment"[All Fields] AND "supplies"[All Fields]) OR "equipment and supplies"[All Fields] OR "device"[All Fields])
9. ("lung"[MeSH Terms] OR "lung"[All Fields]) AND flute[All Fields]
10. positive[All Fields] AND ("exhalation"[MeSH Terms] OR "exhalation"[All Fields] OR "expiratory"[All Fields]) AND ("pressure"[MeSH Terms] OR "pressure"[All Fields])
11. positive[All Fields] AND ("exhalation"[MeSH Terms] OR "exhalation"[All Fields] OR "expiratory"[All Fields]) AND ("pressure"[MeSH Terms] OR "pressure"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])
12. Oscillatory[All Fields] AND Positive[All Fields] AND ("exhalation"[MeSH Terms] OR "exhalation"[All Fields] OR "expiratory"[All Fields]) AND ("pressure"[MeSH Terms] OR "pressure"[All Fields])
13. OPEP[All Fields]
14. "pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR ("chronic"[All Fields] AND "obstructive"[All Fields] AND "pulmonary"[All Fields] AND "disease"[All Fields])
15. "pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR ("chronic"[All Fields] AND "obstructive"[All Fields] AND "lung"[All Fields] AND "disease"[All Fields]) OR "chronic obstructive lung disease"[All Fields]
16. "

Appendix 5. Excluded articles

Study (n=69)	Reason for exclusion
Ambrosino, 1995	Mixed population
Berton, 2015	Study protocol
Bondalapati, 2014	Conference abstract
Butcher, 2007	Mixed population
Cardoso, 2012	Not-OPEP
Cegla, 2010	Critical appraisal
Chakravorty, 2011	Not-OPEP
Christensen, 1990	Not-OPEP
Coppolo, 2016	Retrospective
Cross, 2012	Not-OPEP
D'Abrosca, 2017	Retrospective
D'Cruz, 2018	Retrospective
Daynes, 2018	Conference abstract
Eastwood, 2016	Retrospective
Esquina, 2014	Conference abstract
Gastaldi,2014	Single session treatment
Haluszka, 1990	Not-OPEP
Hardy, 1996	Critical appraisal
Kamimura, 2015	Mixed population
Kamimura, 2017	Mixed population
Kanhere, 2013	Not-OPEP
Khoudigian-Sinani, 2017	Retrospective
Lee, 2008	Retrospective
Li, 2016	Study protocol
Lindemann, 1992	Mixed population
Mahajan, 2011	Mixed population
Mahajan, 2011	Mixed population
Mascardi, 2016	Not-OPEP
Morsch, 2008	Mixed population
Morsch, 2008	Mixed population
Mussche, 2018	Conference abstract
Nct, 2014	Mixed population
Nicolini, 1970	Not-OPEP
Nicolini, 2015	Posters
Nicolini, 2016	Posters
Olseni, 1994	Not-OPEP
Osadnik, 2012	Retrospective
Osadnik, 2013	Conference abstract
Osadnik, 2013	Conference abstract
Osadnik, 2013	Single session treatment
Padkao, 2010	Single session treatment
Panaligan, 2012	Conference abstract

Phimphasak, 2016	Study protocol
Piroddi, 2016	Posters
Pongpanit, 2015	Study protocol
Raafat, 2017	Study protocol
Ragavan, 2012	Laboratory-based studies
Robins, 2015	Not-OPEP
Sethi, 2007	Study protocol
Sheng, 2013	Conference abstract
Spanevello,2015	Study protocol
Suggett, 2015	Conference abstract
Suggett, 2016	Retrospective
Suggett, 2017	Laboratory-based studies
Suggett, 2017	Retrospective
Svenningsen, 2013	Conference abstract
Svenningsen, 2013	Conference abstract
Svenningsen, 2014	Mixed population
Svenningsen, 2016	Conference abstract
Thanh, 2019	Retrospective
Titova, 2005	Mixed population
Usmani ,2013	Study protocol
van der Schans, 1995	Not-OPEP
Varghese, 2014	Study protocol
Voshaar, 1996	Mixed population
Weingarten,2015	Study protocol
Westerdahl, 2017	Retrospective
Weycker, 2017	Retrospective
Wolkove,2002	Single session treatment

Appendix 6. LCM photos on the left shows the monitor model and the connected microphone. The photo on the right shows LCM worn with microphone close to the larynx.

Appendix 7. Instructions for LCM

Cough Monitoring instructions and troubleshooting

- To start the monitor, press the recording button (red button).
- Please fill the sleep diaries attached.
- Keep the monitor on all the time. Please don't stop the recorder.
- If you feel you need to take it off for taking shower, please do the followings:

    1- Take off the microphone as well as the monitor and leave it in your room

    2- Put the microphone and monitor back on when you finish.

- Place the monitor and microphone on a bedside table when you go to bed.
- Put the microphone as well as the monitor back on when you get up in the morning.
- You will supply with 2 extra batteries for the monitor. Please do use them when the monitor batteries indicator shows low batteries. To switch the batteries:

    1- Slide open the battery cover.

    2- Place the batteries in the correct polarity as indicated and close the cover.

    3- Press the recording button (red button) to resume recording cough.

If there are any problems, you can telephone your clinical trial staff……

Mr. Saeed Alghamdi

Return monitor Date .....……Time……

By post / hand into trial centre.

Appendix 8. Sleep monitoring instructions.

Sleep monitoring instructions and troubleshooting

- The device should be worn around the waist, at the middle of the lower back. The engraved McRoberts logo should be readable, and the waist belt should be on the inside. It can be worn directly on the skin or over a layer of clothes.
- Keep the monitor on you all the time except when you need to take a shower.
- The monitor will be prepared and turn on at the clinical site. If you are taking shower, please do the followings:
    1. Take off the monitor and leave it in your room
    2. Put the monitor back on when you finish

If there are any problems, you can telephone your clinical trial staff……

Mr. Saeed Alghamdi

Patient **NAME**:

Patient ID:

Telephone:

Start monitoring time: Date……. Time……

Date the monitored taken: Date ……. Time…….

Return monitor Date .....……Time……

By post / hand into trial centre.

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