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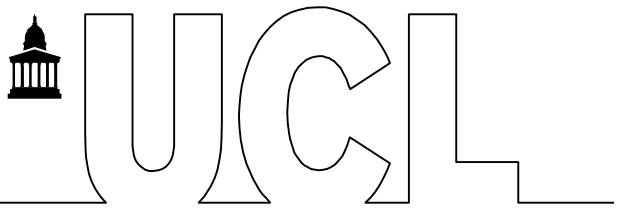

Domiciliary Monitoring to Predict Exacerbations of COPD

A thesis submitted for the degree of Doctor of Philosophy

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Candidate

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Declaration

I Ahmed Al Rajeh confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

Date:

Abstract

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a common, long-term condition that is usually caused by cigarette smoking. In addition to daily symptoms and limitation in activities, patients are prone to chest infections ('exacerbations'). These are a significant problem: unpleasant for patients, and sometimes severe enough to cause hospital admission and death. Reducing the impact of exacerbations is very important. Previous studies have shown that earlier treatment of exacerbations results in faster recovery, and reduced risk of hospital admission. Helping patients to better detect exacerbations early is therefore important. This PhD focuses on measuring overnight heart rate and oxygen saturation, which we hypothesised would provide the best chance of detecting COPD exacerbations earlier than changes in symptoms.

Aim: To evaluate the potential of monitoring physiological variables to provide earlier detection of exacerbations of COPD.

Methods: Firstly, a systematic review was conducted to assess the existing literature on predicting exacerbations of COPD by monitoring physiological variables. Next, two clinical tele-health datasets were accessed, from two different NHS services in London, to report the impact of false alarms on tele-health service, and to examine the feasibility of using downloadable data from home non-invasive ventilation to detect exacerbations resulting in hospitalisation. National and international surveys were conducted to explore the techniques that have been used by healthcare providers on how to customise tele-health alarm limits for each individual, and to explore healthcare providers' perceptions of tele-health for COPD.

These preliminary projects enabled me to formulate my research question and main PhD hypothesis, tested using a prospective randomised controlled trial. Patients were randomised into two groups (one measured physiology only in the morning versus overnight continuous measurement) and patients were monitored for up to six months or the first exacerbation, whichever was sooner. Patients' acceptance of continuous overnight monitoring was assessed at the end of the study.

Results: Existing studies that used physiological variables were small and heterogeneous using different variables and different protocols. The majority of medical alarms received by tele-health teams are false. Most patients reported a positive acceptance of being monitored overnight. Continuous overnight monitoring identified changes at exacerbation earlier than once-daily monitoring, and earlier than symptoms. Changes in physiological variables were correlated with changes in symptoms during non-stable phases. There is widespread UK national and international use of tele-health monitoring physiological variables in COPD without sufficient evidence base.

Conclusion

Monitoring physiological parameters may be useful in assisting earlier detection of COPD exacerbations but further, robust studies are required to confirm this. A particular challenge is how to set alarm limits for individual patients given the heterogeneity inherent in COPD and COPD exacerbations.

Impact statement

The three key findings of this thesis are: a) there is widespread international use of tele-health in COPD, b) in the absence of current guidelines about how to use tele-health in COPD, different practioners are measuring different variables in different ways and using different mathematical algorithms, and c) overnight monitoring gives earlier detection of COPD exacerbation changes than once-daily monitoring and variables change prior to presentation with exacerbation. The impact on healthcare systems is therefore to question the current use of tele-health, and in particular to ensure practioners using tele-health should have clear aims and methodology, as inappropriate use will have an adverse impact on both healthcare systems and patients. Findings from this PhD emphasise the need for researchers to conduct further high-quality studies in tele-health and the use of physiological variables to predict exacerbations. In particular, having demonstrated the potential utility of overnight physiological monitoring to detect exacerbations, future collaborations should be established with technology and engineering departments and industry with the aim of developing a product that may help to assist early detection of COPD exacerbations and thus improve current practice and, ultimately, the lives of those living with COPD. Findings have been and/or will be disseminated through scientific journals, conferences, and social media to maximise the reach of our research.

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Abbreviations

ABG	Arterial Blood Gas
ABPM	Ambulatory Blood Pressure Monitoring
ACOS	Asthma-COPD Overlap Syndrome
AMED	Allied and Complementary Medicine Database
ARF	Acute Respiratory Failure
AUC	Area Under the Curve
AVAPS	Average Volume-Assured Pressure Support
BiPAP	Bilevel Positive Airway Pressure
BMI	Body Mass Index
BP	Blood Pressure
BVR	Bronchoscopic Volume Reduction
°C	degrees Celsius
CAT	COPD Assessment Test
CHCF	California Health Care Foundation
CINAHL	Cumulative Index of Nursing and Allied Health Literature

CMS	Centre for Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
DNA	Deoxyribonucleic Acid
Embase	Excerpta Medical Database
EPAP	Expiratory Positive Airway Pressure
ESS	Epworth Sleepiness Score
EXACT	Exacerbation of Chronic Pulmonary Disease Tool
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GOLD	Global initiative for Obstructive Lung Disease
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HRQL	Health Related Quality of Life
HRSA	Health Resources and Services Administration
ICS	Inhaled Corticosteroids
IPAP	Inspiratory Positive Airway Pressure
IQR	Interquartile Range

L	Liter
LABA	Long-Acting Beta$_2$ Agonist
LAMA	Long-Acting Antimuscarinic
LTOT	Long-Term Oxygen Therapy
LVRS	Lung Volume Reduction Surgery
MCID	Minimum Clinically Important Difference
Medline	Medical Literature Analysis and Retrieval System Online
mHealth	Mobile Health
min^{-1}	per minute
MMP12	Matrix Metalloproteinase 12
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
OSA	Obstructive Sleep Apnoea
PAV	Proportional Assisted Ventilation
PEEP	Positive End Expiratory Pressure
PEF	Peak Expiratory Flow
PFT	Pulmonary Function Test

PR	Pulmonary Rehabilitation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome;
RPM	Remote Patient Monitoring
RR	Respiratory Rate
S/T	Spontaneous/Time mode
SABA	Short-Acting $Beta_2$ Agonist
SAMA	Short-Acting Antimuscarinic
SD	Standard Deviation
SpO_2	Oxygen Saturation
TB	Tuberculosis
%trigg	Percentage of Respiratory Cycles Triggered
UK	United Kingdom
US	United States
Ve	Minute ventilation
Vt	Tidal Volume

WHO	World Health Organisation

1. Introduction

This introduction describes the background to key subject areas investigated in this PhD thesis: Chronic Obstructive Pulmonary Disease (COPD) and, in particular, COPD exacerbations and how these may be detected earlier via home monitoring of physiological variables including tele-health, and non-invasive ventilation.

1.1 Chronic Obstructive Pulmonary Disease (COPD)

The Global initiative for Obstructive Lung Disease (GOLD) strategy document has defined COPD as *"a common preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases"* (1). Cigarette smoke, biomass, or other noxious agents trigger an inflammatory response in the lung (2). COPD develops due to an excessive cumulative exposure to such risk factors such that the inflammation becomes chronic. The development of COPD also requires individual (genetic) susceptibility, the best example of which is Alpha-1 antitrypsin deficiency (3). Chronic inflammation may cause narrowing of the small airways and permanent lung parenchymal destruction **(COPD)**. COPD is heterogeneous. Submucosal bronchial gland mucus production will increase and cilia function will decrease; thus, there is excessive accumulation of mucus **(Chronic Bronchitis)** (1, 2) (Figure1). Chronic bronchitis is defined clinically as a *"chronic productive cough for 3 months in each of 2 successive years in a patient in whom other causes of productive chronic cough have been excluded"* (2).

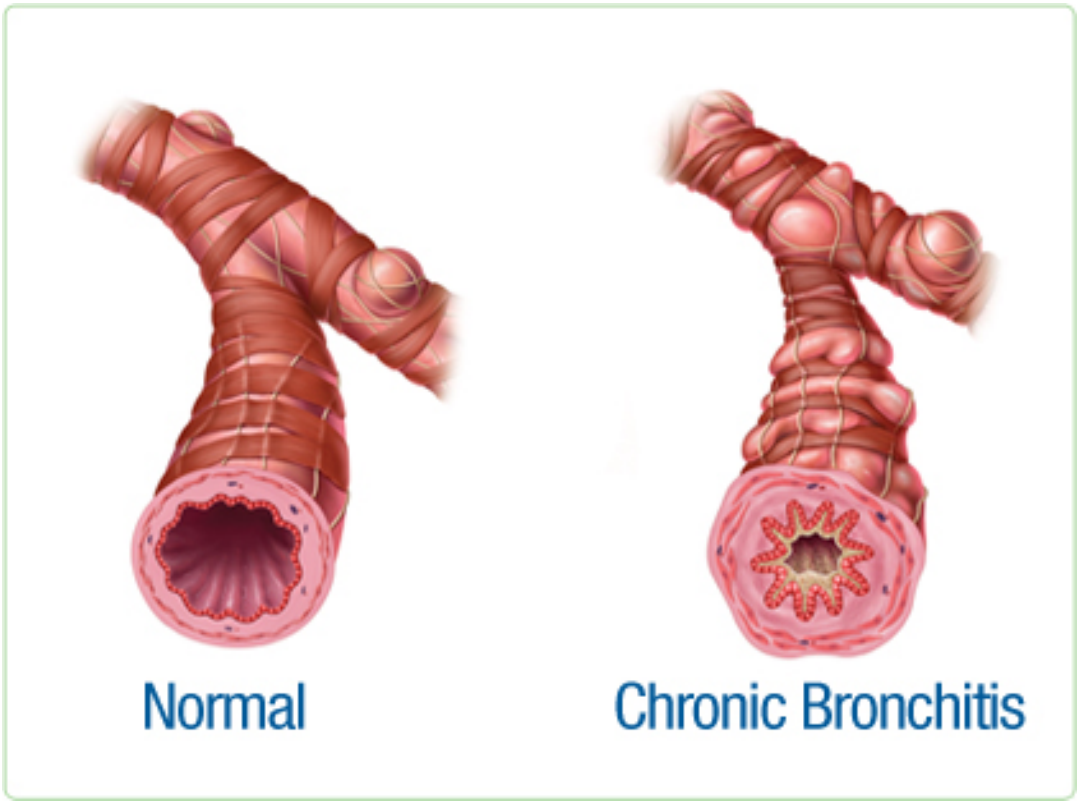

Figure 1. Normal airway versus airway affected by chronic bronchitis (4). Note the mucus gland hypertrophy and luminal accumulation of mucus.

With regard to lung parenchymal destruction, the distal airways and alveoli will be permanently enlarged and destroyed, which may also involve the destruction of pulmonary capillaries **(Emphysema)**. As a consequence, the small airways collapse during expiration, and this will lead to air trapping (hyperinflation) and shortness of breath (1, 2) (Figure 2), initially on exercise and with more advance disease even at rest.

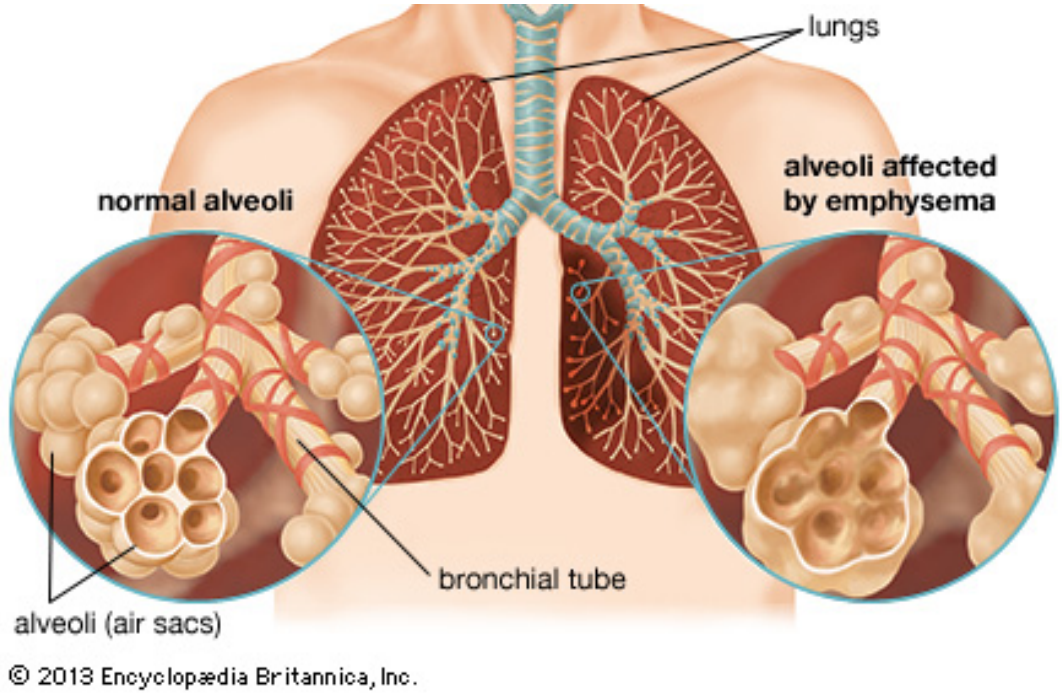

Figure 2. Normal alveoli compared to Emphysema (5). Emphysema represents loss of alveoli.

1.1.1 Aetiology

The majority of COPD occurs due to long-term exposure to an irritant substance that affects the lungs (1). However, there are various risk factors related to the development of COPD and to the prognosis of the disease:

1.1.1.1 Cigarette smoking

Cigarette smoking is the most important cause of COPD in the developed world. A high percentage of people diagnosed with COPD have a history of smoking, indicating that people who smoke are at a higher risk of developing COPD (6). Yet, cigarette smoking is not the only factor that can cause COPD, and not all heavy smokers develop COPD. Burrows et al. noted that lung function decline (Forced Expiratory Volume in 1 second (FEV_1)) is associated with smoking (pack year) history (7). Other studies have shown that smokers are more vulnerable to

symptoms, disease worsening, and lung cancer when compared to non-smokers with chronic airflow limitation (1).

1.1.1.2 Occupational exposure

According to the American Thoracic Society, the impact of occupational exposure, which includes exposure to fumes, chemicals, and organic/nonorganic dusts (1) constitutes 10-20% of cases of COPD. In a study conducted in 2015, occupational exposure impact was investigated in 1075 participants (COPD = 721 participants, non-COPD smokers = 354 participants) (8). Among the COPD participants, occupational exposure was correlated with a higher risk of exacerbation, decreased quality of life and poor outcomes. Hnizdo investigated the percentage of COPD in the United States attributed to occupational exposure in 9823 participants. The researchers reported that the overall share was 19.2%, and 31.1% among participants who had never smoked (9). Based on the literature, the impact of cigarette smoking and occupational exposure is high; thus, appropriare prevention strategies are needed (10).

1.1.1.3 Indoor and outdoor pollution

Indoor and outdoor pollution may also have an impact on the development of COPD (1). Outdoor air pollution, such as fuel pollution, is associated with a reduction of lung function in existing lung disease sufferers, even though the relative risk is not clear (11). Exposure to indoor pollution, such as burning animal dung, crop residues, coal, wood, and biomass to cook and to heat, affects more than three billion people globally, and researchers have suggested that better indoor ventilation and use of cleaner fuels could have a great impact on the reduction of COPD risk (1, 11).

1.1.1.4 Genes

Genetic polymorphisms contribute to COPD risk. Studies have shown that smokers with a family history of severe COPD are at a high risk of developing airflow limitation (1). Alpha-1 antitrypsin deficiency is a genetic disorder which increases the risk of developing COPD (1, 2, 6). A low concentration of alpha-1 antitrypsin (influenced by genetic polymorphisms in the SERPINA1 gene) in the blood was found to be associated with early COPD symptoms onset and reduction of lung function (12). Although alpha-1 antitrypsin deficiency is the most common identifiable cause it accounts for only a small proportion of COPD cases. The gene encoding matrix metalloproteinase 12 (MMP12) gene has found to be associated with positive lung function and decreased risk of COPD in adult smokers (13).

1.1.1.5 Age and Gender

COPD is more common in older people, but as a risk factor, it is unclear because of the uncertainty of whether changes are due to the decline in overall health status as an individual ages, or due to the amount of accumulated exposure that the individual had been exposed too. With regard to gender, even though past statistics show that men are more prone to developing COPD than women; recent studies have reported that both men and women are at equal risk, due to behavioural changes in smoking patterns (1, 2, 6).

1.1.1.6 Lung growth

Premature birth and childhood exposures affect lung development. Evidence has shown that those born prematurely may develop airway obstruction (1). Barker evaluated the impact of birth weight and respiratory infection during childhood on lung function. In 825 participants, higher FEV_1 was associated with greater birth

weight, and respiratory infections were associated with lower FEV_1 (14). Moreover, results of lung function tests from premature children were significantly different compared to tests in normal children, suggesting that a strategy should be considered to monitor the development of chronic respiratory disease (15).

1.1.1.7 Asthma

Asthma could be considered a risk factor for COPD. According to Vonk et al., 16% of 228 asthmatic people developed COPD (16). Furthermore, a large prospective study, involving 3099 participants and followed for 20 years, noted that asthmatic patients are at a 12.5-fold higher risk of developing COPD (17). Although pathologically asthma and COPD are two different respiratory diseases, clinical differentiation can be difficult once asthmatics acquire COPD (17, 18) with the development of Asthma-COPD Overlap Syndrome (ACOS) (19).

1.1.1.8 Chronic bronchitis

Individuals diagnosed with chronic bronchitis have been found to be at a high risk of acquiring COPD. A large study conducted on 4427 participants in 2016 noted that the presence of chronic mucus hypersecretion was associated with acceleration in FEV_1 decline (20). Guerra et al. reported that 42% (41/97) of participants diagnosed with chronic bronchitis acquired COPD. In another study, the risk of a chronic bronchitis patient developing COPD was found to be 94% in a study of 1410 participants (21).

1.1.1.9 Infections

Respiratory infections during childhood have been reported as having a potential association with the risk of later COPD (1). Previous literature has documented that Human Immunodeficiency Virus (HIV), Tuberculosis (TB), and

other infections caused by double-stranded DNA viruses are associated with COPD. In a systematic review conducted in 2015, the authors reported that the diagnosis of COPD was strongly correlated with the existence of a previous history of TB (22).

1.1.2 Epidemiology

1.1.2.1 Global

COPD imposes a global burden on individuals and healthcare systems. According to the World Health Organisation (WHO), in 2016, 251 million individuals were living with COPD worldwide (23). The number of patients who died from COPD was 3.17 million in 2015, which makes it the fourth leading cause of death (23, 24). Data suggest COPD will become the third leading cause of death by 2030 if no response is taken, with a death rate of 4.5 million per year (25, 26). COPD is therefore a highly prevalent global disease. The economic impact of COPD equates to $2.1 trillion in treatment costs and employment impact, which is expected to double by the year 2030 (27).

1.1.2.2 United Kingdom (UK)

According to the British Lung Foundation, 1.2 million individuals are currently diagnosed with COPD in the United Kingdom (UK), and there are many more undiagnosed cases – the ‘missing millions’ (28). Snell et al. reported that 29,776 patients died because of COPD in 2012, which makes it the fifth leading cause of death in the UK (28, 29). The annual direct cost of COPD is reported to be nearly one billion pounds, with more than one million bed days and 140,000 hospital admissions annually (29). This information translates into the need for better interventions to mitigate the burden of COPD.

1.1.2.3 Kingdom of Saudi Arabia (KSA)

The prevalence of COPD in Saudi Arabia has not been well investigated. In 2015, Alghobain et al. reported an estimated COPD prevalence in Riyadh using a cross-sectional survey (30). Findings were stratified according to severity (GOLD COPD grade 1&2), and gender. 784 out of 866 participants completed a questionnaire and underwent spirometery. They reported that 4.2% had COPD GOLD 1, and 3.7% COPD GOLD 2. Males were higher in both groups. However, this study has limitations: the stratification was limited to GOLD grade 1&2 only; the sample was taken from only one city; age was limited to adult ≥40 years old; and only cigarette smokers were considered. Therefore, these data cannot be considered representative, and better-designed studies are needed.

1.1.3 Diagnosis

The GOLD report suggests that COPD testing should be performed if one or more of the following indications are present:

1- Dyspnoea.

2- Chronic cough.

3- Chronic sputum production.

4- History of exposure to COPD risk factors.

If one or more of the above indications appear, a Pulmonary Function Test (PFT), specifically spirometry, is required to confirm the diagnosis (1, 2).

1.1.3.1 Pulmonary Function Testing

PFTs encompass a number of measures to assess lung conditions (31). However, to diagnose COPD, the healthcare provider must evaluate post-bronchodilator, quality-assured Vital Capacity (or Forced Vital Capacity, (F)VC),

Forced Expiratory Volume in 1 second (FEV_1), and FEV_1/(F)VC ratio. These measures can be obtained via spirometry, which requires a maximal deep inspiration followed by quick and hard expiration, using a volume or flow spirometer. The volume spirometer (first generation of spirometer) has a reservoir that measures the amount of volume exhaled from the lungs, whereas the flow spirometer measures the flow coming out from the lungs and then calculates the volume electronically (32). Predicted values are based on each individual's age, height, race, and sex. Three attempts should be performed after bronchodilator administration. The FEV_1 value difference between the three attempts should be within 5%, or 150ml. A post-bronchodilator ratio of FEV1/(F)VC <70% and/or the lower-limit of normal (LLN) confirms the presence of COPD (1, 2, 31).

1.1.4 Assessment

The FEV_1 value is also used to evaluate the severity of COPD-related airflow obstruction (disease grade). The GOLD report has published the recommended scale for classification based on FEV_1 values obtained from spirometry (Table 1).

Table 1. Classification of COPD severity (1). All require low ratio.

GOLD grade	Severity	FEV_1 % predicted
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted/acute respiratory failure

The determination of disease grade previously influenced the prescription of medication (1). Whilst spirometry is required to diagnose COPD, the GOLD report now suggests different assessment tools should determine the pharmacological management approach in COPD (1, 2). This can be achieved via the established "ABCD" assessment tool by GOLD. The ABCD assessment tool is a scheme that helps in assessing the patient's airways from two additional aspects: symptom burden (Medical Research Council (MRC) dyspnoea scale or COPD Assessment Test (CAT) questionnaire); and exacerbation/hospitalisation history. Based on each score, the patient will be allocated to one of the ABCD groups (Figure 3).

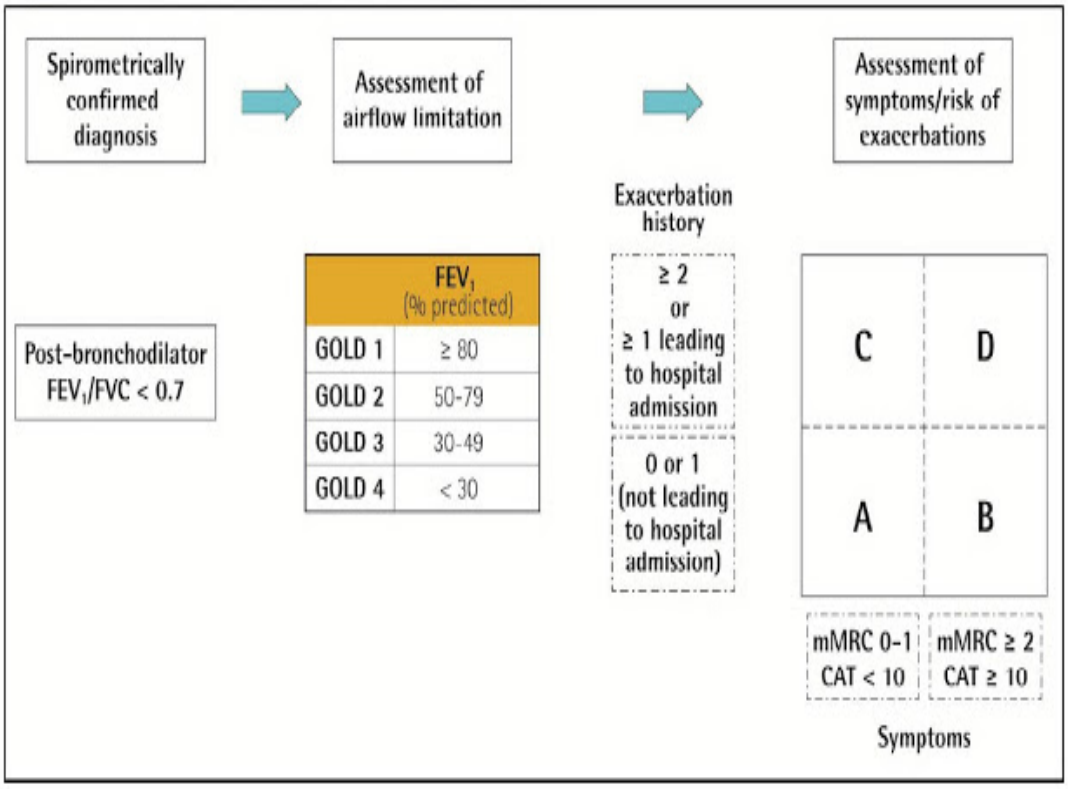

Figure 3. The refined ABCD assessment tool for COPD (33).

1.1.5 Management

Studies have shown that COPD outcomes can be improved with disease management. According to the World Health Organisation (WHO), the goal of COPD management is to prevent disease progression, exacerbations, complications, and to improve exercise capacity and health status (34). Management of COPD can be divided into two parts, stable disease and exacerbation:

1.1.5.1 Management of stable COPD

1.1.5.1.1 Monitoring and follow up

Longitudinal follow-up with re-assessment allows changes to the management over time, based on the patient's current condition, aiming to alleviate COPD complications (1, 2). Current guidelines support the importance of routine evaluation of lung function, exacerbation frequency, exercise tolerance, symptoms and comorbidity. These factors are associated with an increased rate of exacerbation, hospitalisation, and mortality (1, 35, 36).

1.1.5.1.2 Smoking cessation

Smoking cessation (and exposure reduction for occupational/biomass COPD) is considered the most important management element as it affects COPD progression. In 1977, Fletcher and Peto suggested that the average rate of decline in lung function could return to normal as a result of quitting smoking, which highlighted the importance of smoking cessation to all patients with COPD (37) (Figure 4). Moreover, the Lung Health Study, conducted on 5887 COPD patients in the United States (US) and Canada, showed that smoking cessation decreased the FEV_1 decline rate significantly when compared to a control group (38). Also, in 2004,

Willemse et al. reported that smoking cessation was associated with positive outcomes on respiratory symptoms and lung function (39).

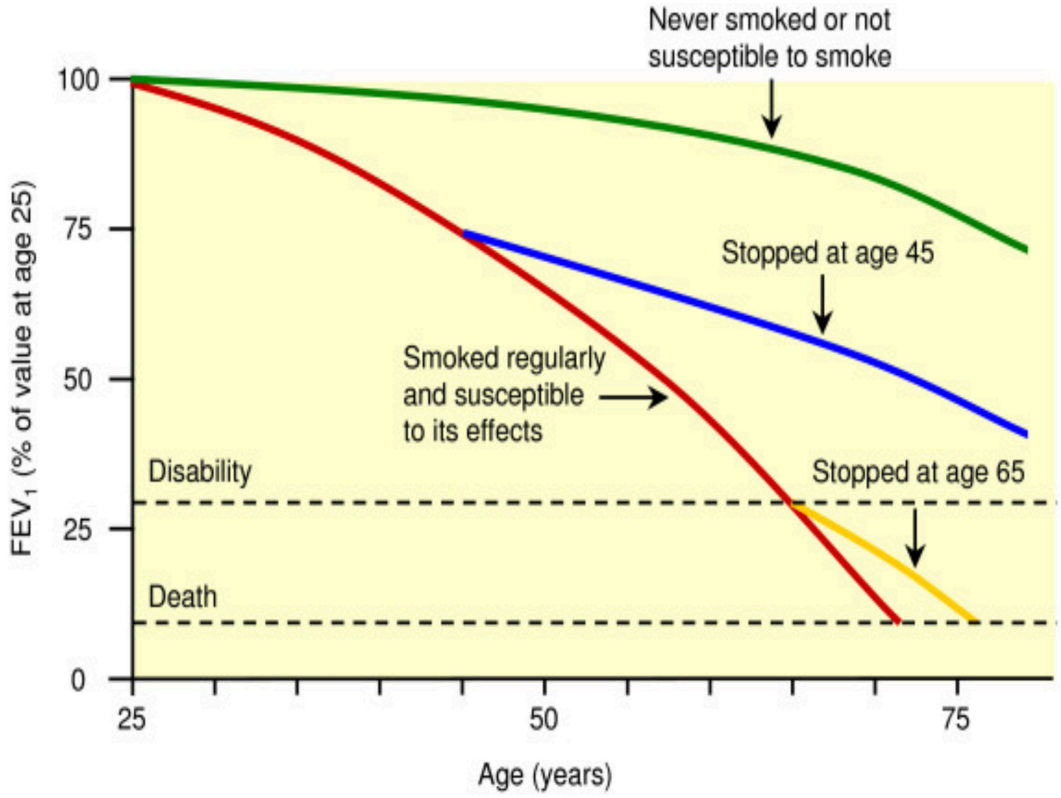

Figure 4. The difference in FEV_1% decline between non-smokers, ex-smokers and susceptible smokers (37, 40).

1.1.5.1.3 Pulmonary rehabilitation

Pulmonary rehabilitation (PR) is a comprehensive training program that integrates different management elements such as exercise tolerance and capacity, disease education, nutrition, etc. All contribute to the improvement of COPD outcomes (1, 2, 6). In 2015, McCarthy conducted a systematic review to summarise the effect of pulmonary rehabilitation on COPD patients. They found that patients who underwent PR had significant improvements in quality of life, dyspnoea, and exercise capacity (41).

1.1.5.1.4 Vaccination

Influenza vaccination has been noted to be associated with a reduction in hospitalization rate, outpatient visits, exacerbations rate, and mortality (42, 43). Further, a reduction of pneumonia incidence was associated with the administration of **Pneumococcal vaccine** (44).

1.1.5.1.5 Pharmacologic therapy

The use of therapeutic drugs in COPD patients should be based on the current disease grade, and on a desired goal (1). It is known that pharmacological therapy has an impact on respiratory symptoms, exacerbations, quality of life and exercise tolerance (38, 45), but drugs have not conclusively been shown to affect FEV_1 decline rate or mortality (1). The type of medication prescribed varies according to the purpose of use. **Bronchodilators** (short-acting $beta_2$ agonists (SABA) and long-acting $beta_2$ agonists (LABA), and short-acting antimuscarinics (SAMA) and long-acting antimuscarinic (LAMAs)) are mainly used for symptom relief and FEV_1 improvement (46, 47). The use of bronchodilators in stable COPD patients has shown positive outcomes not only in FEV_1 and symptom improvement, however, but also in decreasing exacerbation rate, and hospital admission rates. **Anti-inflammatory** agents (inhaled corticosteroids (ICS)) may also be used to reduce exacerbation rates (48). However, moderate to very severe COPD, and frequent exacerbator patients were found to benefit more from corticosteroids (1) and most recent data suggest that benefit of ICS can be predicted from measurement of blood eosinophils (49). In addition, **antibiotics** in stable COPD patient could be used as a prophylactic approach, as they have been associated with in some studies to result in fewer exacerbations in moderate to severe COPD patients (50). **Mucolytics** are

another class that can be prescribed to mitigate the burden of COPD. These facilitate sputum expectoration (51). **Methylxanthines (**limited by toxicity) have been correlated with better inspiratory muscle outcomes. The most common methylxanthine used is Theophylline. In a study conducted on 943 stable COPD patients using theophylline with salmeterol, FEV_1 and dyspnoea improved significantly compared to the use of salmeterol alone (52). **Combination bronchodilators** might be more effective than a single agent. Recent studies have shown that the combination of LABA and LAMA together are associated with better FEV_1, respiratory symptoms, and quality of life when comparing the use of each class alone (1). Some researchers have studied the impact of **triple inhaled therapy** (LAMA/LABA plus ICS) on lung function and exacerbation frequency. Lipson et al., in 2018, were able to show that the use of triple inhaled therapy was associated with a lower moderate/severe rate of exacerbations compared to dual therapy, with a rate of: 0.91 exacerbation/year vs 1.07 exacerbation/year ($p<0.05$), respectively (53). With regard to lung function, the researchers also found that patients who were receiving the triple inhaled therapy had a better improvement in FEV_1, with a difference of 97 ml compared to patients who were on dual therapy ($p<0.0001$).

1.1.5.1.6 Other therapeutic approaches

The survival rate of severe COPD with chronic respiratory failure and resting hypoxemia is increased with the administration of **Long-Term Oxygen Therapy** (LTOT) for more than 15 hours/day (1). **Ventilatory support** can also have benefits for COPD exacerbations with acute (hypercapnoeic) respiratory failure, and COPD with Obstructive Sleep Apnoea (OSA) patients as it has been associated with a reduction in hospitalisation risk, and a better survival rate (54). The use of home

ventilatory support has shown some benefits in COPD. Melloni et al., in 2018, reported that patients managed by non-invasive ventilation with/without long-term oxygen therapy have a better ten-year survival rate than those who were receiving LTOT only (32.3% vs 11.8% $p<0.05$), respectively (55). According to a multicentre clinical trial conducted on 195 stable COPD patients by Kohnlein et al., the one-year mortality rate of patients who did not receive home NIV (33%) was greater than patients who were on home NIV (12%) ($p<0.05$) (56). They also reported that patients on home NIV had improved quality of life, FEV_1, exercise capacity, and arterial carbon dioxide outcomes when compared to the control group. In addition to the administration of oxygen therapy or ventilator support, **surgical intervention** might be considered in some COPD patients (selected patients). Lung Volume Reduction Surgery (LVRS) in severe emphysema has been found to increase lung recoil and improve respiratory muscles due to hyperinflation reduction (57). However, LVRS was associated with a high mortality rate or no difference compared to patients in the usual care arm (58) unless patients were carefully selected. It can now be achieved using Bronchoscopic Volume Reduction (BVR) interventions, such as the endobronchial valve placement procedure (59). Bullectomy is another surgical intervention that may increase exercise capacity and decrease dyspnoea in very severe emphysema patients (60). Moreover, lung transplant surgery in severe COPD patients is associated with better quality of life and exercise capacity. Double lung transplant showed a better survival rate compared with single lung transplant but outcomes after transplant remain poor compared to transplant in other solid organs (1, 60).

1.1.5.2 Management of non-stable COPD (exacerbations)

1.1.5.2.1 Definition

According to the GOLD report, *"COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy"* (1). Exacerbations could be classified as mild, moderate, or severe (Table 2).

Table 2. Exacerbation classification and definition.

Classification	Definition
Mild	Exacerbations treated with bronchodilators.
Moderate	Exacerbations treated with bronchodilators + antibiotic or/and corticosteroid.
Sever	Exacerbations leading to hospitalisation/ER visit.

However, some scientists and healthcare providers have used different definitions and classifications for COPD exacerbations such as the one used by Anthonisen et al.: *"an increase of two major respiratory symptoms (dyspnea, sputum purulence, sputum volume) or one major and one minor respiratory symptoms (cold, sore throat, wheeze, cough) for two consecutive days"* (61, 62). Standardisation of the definition and classification may enhance the clinical management of COPD exacerbation and COPD research design (63). A challenge is that changes in symptoms in a patient with COPD may be due to other diseases such as heart failure, or anxiety.

1.1.5.2.2 Aetiology of exacerbations

Although bacterial infections and exposure to pollution can cause an onset of COPD exacerbation, respiratory viral infection is the most common cause, particularly rhinovirus (64). Researchers have reported that 50-70% of exacerbations are because of viral and bacterial infections (65), whilst 10% are due to

environmental pollution (66). However, Connors et al. have shown that the aetiology of 30% of exacerbations is unknown (67). Exacerbations of COPD are associated with an increased inflammatory response in the lung (and systematically in the blood). Bhowmik et al. investigated sputum cell counts and cytokines (interleukin-6 and interleukin-8) in 57 COPD patients before and during an exacerbation. They noted that sputum inflammation increased significantly during the exacerbation phase compared to the stable phase (68). Further, Papi et al. found that in 64 COPD patients, the numbers of neutrophils in the blood and sputum were increased during exacerbation (69). In another study conducted on 145 COPD patients by Bafadhel et al, eosinophil levels in sputum were increased during exacerbations (70).

1.1.5.2.3 Burden of COPD exacerbations

Exacerbations impose a huge burden on an individual, and can be life-threatening (1, 71). Evidence has shown that exacerbations are associated with morbidity and mortality (72). Furthermore, exercise capacity and lung function measures in COPD patients decrease because of exacerbations (73). The number of exacerbations per year for each individual has become vital for COPD assessment, classification and management. Exacerbation frequency can be divided into: frequent (2 or more exacerbations in the past 12 months), and infrequent (fewer than 2 exacerbations in the past 12 months) (74). Seemungal et al. noted that “frequent exacerbators” had significant reduction in quality of life when compared to infrequent exacerbators (75). Others, moreover, have noted that frequent exacerbators are prone to a greater FEV_1 decline over time (76). The majority of COPD exacerbations last for up to ten days (77). Aaron et al. found that recovery time from exacerbations might be influenced by two patterns of exacerbation onset: sudden onset or gradual

onset. They found that gradual exacerbations are associated with longer recovery time, but are less severe compared to sudden exacerbations (77). Therefore, in addition to COPD being heterogeneous, exacerbations are heterogeneous too.

1.1.5.2.4 Management

The goal of treating COPD exacerbations is to lower the impact of the current exacerbation episode and prevent other episodes (1). Management should be based on the type of exacerbation (mild, moderate, or severe) (1). Short-acting bronchodilators used in the management of stable COPD can also be used for exacerbations (by an increase in dose and/or frequency) as this helps in relieving respiratory symptoms (78). However, when an exacerbation does not respond to this alone, the use of antibiotic or systemic corticosteroids is advised (78). Ram et al. reported that the use of antibiotics in moderate to severe COPD patients to treat exacerbations could reduce short-term mortality rate by 77%, and decrease sputum purulent by 44% (79). Further, the use of antibiotics has been noted to be associated with faster recovery (80). In addition, in severe exacerbations, the administration of oxygen might be required with hypoxemic patients, whereas the use of non-invasive ventilation (NIV) is necessary in the presence of hypercapnia (life threating respiratory failure). Furthermore, the use of invasive ventilation might also be considered in some situations, such as NIV failure, aspiration, etc. (1).

1.2 Non-invasive ventilation (NIV)

1.2.1 Definition and history

NIV can be defined as the delivery of ventilatory support non-invasively to a patient through a variety of interfaces attached to the upper airway. NIV comes in two forms of administration: negative pressure ventilation and positive pressure ventilation (81). The administration of negative pressure ventilation, a historic technique, is performed by applying two cycling pressures around the thorax to create a pressure gradient (i.e. iron lungs & chest cuirass). It was first used in 1928 on patients diagnosed with poliomyelitis, and by the 1950s on acute and chronic COPD patients as it was found to be associated with a better survival rate. However, in 1952, the use of negative ventilation stopped after invasive ventilation started to become more popular, especially in acute settings, and negative pressure ventilation was limited to home use. In 1990, the revolution of applying positive ventilation pressure non-invasively was introduced, and this has continued since then. This form of ventilation has been increasingly used in acute and chronic respiratory settings over the past years (82). The idea of Bilevel Positive Airway Pressure (BiPAP) ventilation is the administration of two levels of pressures that assist ventilation and oxygenation: Inspiratory Positive Airway Pressure (IPAP) and Expiratory Positive Airway Pressure (EPAP). IPAP is the pressure delivered by the ventilator during the inspiratory phase to assist the delivery of the desired tidal volume, which is related to the IPAP level (a higher IPAP level means a higher tidal volume), whereas EPAP is the pressure delivered during the expiratory phase to improve oxygenation (82).

1.2.2 Purpose of use

NIV can be used with many patients in many acute and chronic settings. Evidence has suggested that the physiological purposes of NIV include improved oxygenation, optimised ventilation, and a decrease in the work of breathing (81, 82).

1.2.3 Non-invasive ventilation with COPD

NIV has been used with COPD in the acute exacerbation setting and in the stable home management setting. It has been found that NIV can improve oxygenation, ventilation, and muscle effort for inspiration in stable and unstable COPD patients (83, 84). Kohnlein et al, have shown, from a multi-centre study conducted on 195 stable severe COPD patients, that the use of NIV after one year significantly improved the survival rate, $PaCO_2$ (20% reduced from baseline), FEV_1, 6-minute walk test, and Health Related Quality of Life (HRQL) (85). Moreover, in a recent randomised clinical trial conducted by Murphy et al., 116 persistent hypercapnic COPD patients (post-exacerbation) were investigated for the impact of administering NIV therapy after two to four weeks exacerbation resolution on readmission and death over one year. In the trial, both groups received oxygen therapy, but only patients who were in the experimental arm (n=57) also received NIV. The researchers reported that the median time to readmission or death in the experimental group increased (4.3 months vs 1.4 months, $p<0.05$), and the median rate of exacerbation per year decreased significantly (3.8 exacerbation/year vs 5.1 exacerbations/year, $p= 0.02$) (86). The health-related quality of life was assessed at week six and at week 12, using two different questionnaires. In both periods (week 6 and week 12), the improvement of health-related quality of life in the experimental arm was greater ($p<0.05$).

The use of NIV in the acute COPD setting has also been reported to be effective in selected patients (87). In a randomised control trial conducted to compare NIV intervention with usual care on 30 acute hypercapnic COPD patients, NIV was associated with a significant improvement of Arterial Blood Gas (ABG) results (PaO_2, $PaCO_2$, pH), breathing rate, and length of hospital stay (88). Furthermore, Brochard et al. reported that NIV has a significant impact on the need for intubation (26% vs 74% $p<0.001$), length of stay (23 -/+17 days vs 35 -/+33 days), and inpatient mortality rate (4% vs 12%) in acute COPD patients when compared to standard care with no NIV (89). In another trial, conducted by Plant in 2000, inpatient mortality was lower in patients who had received NIV compared to usual care (10% vs 20%, $p= 0.05$) (90), However, a retrospective study conducted in 2013 reported that the inpatient mortality rate in COPD patients with respiratory failure who received NIV was 24.3% (91).

1.2.4 Non-invasive ventilation modes

Bi-level positive airway ventilation can be delivered in two different forms: volume-targeted or pressure-targeted ventilation (92). In volume-targeted ventilation, the healthcare provider sets the tidal volume needed to be delivered to the patient; flow rate in this form of ventilation depends on inspiratory time, which can affect patient comfort if the patient respiratory demand is not met (82). However, this type of ventilation has shown similar effectiveness to pressure-targeted ventilation on COPD patients, even though Girault et al. reported that patients on volume-targeted ventilation reported higher inspiratory discomfort (84). With pressure-targeted ventilation, each breath delivered to the patient is based on a pre-set positive pressure level. The patient's mean airway

pressure should be kept constant to achieve the desired tidal volume (82, 93). Pressure-targeted ventilation has been found to be associated with better patient tolerance, comfort, and leak compensation (82). A lot of different ventilator modes have been introduced under these forms to optimise patient-ventilator interaction. One of these modes is Proportional Assisted Ventilation (PAV). This mode has been reported to be more comfortable to patients as the ventilation delivered is based on the patient's ventilator demand and efforts. PAV was applied in stable COPD patients and associated with better gas exchange and dyspnoea (94). Furthermore, it has shown its effectiveness in decreasing the patient's work of breathing, effort, and optimal minute ventilation achievement (95-97). With PAV mode, the level of Inspiratory Positive Airway Pressure (IPAP) is controlled by the patient's effort only, which in some cases is not the appropriate mode as the IPAP level will not respond to changes in the respiratory system, such as airway resistance and compliance (82). Another mode recently introduced is Average Volume-Assured Pressure Support (AVAPS). AVAPS is a dual mode of volume and pressure ventilators (a hybrid mode) *"that associates a tidal volume target to PSV by means of an algorithm estimating the patient's tidal volume over several breaths and calculating the variation in IPAP necessary to achieve the target tidal volume" (82)*. According to the study of Amato et al. conducted on acute ventilatory failure patients, AVAPS was found to be associated with a better intrinsic Positive End Expiratory Pressure (PEEP) level due to inspiratory impedance reduction, improved lung compliance, mean inspiratory flow, and tidal volume when compared with volume-assisted ventilation (98). Furthermore, Claudett et al.

noted that COPD exacerbated patients receiving BiPAP-AVAPS mode in the emergency department had no difference in length of stay or NIV duration compared with patients receiving BiPAP-Spontaneous/Timed mode (S/T). Yet, patients on AVAPS mode had faster consciousness recovery and better arterial blood gas results (99).

1.3 Tele-Health

'Tele' is a Greek derivative that means "in distance" or "far off"; thus, tele-health is a health care service provided to patients at a distance. The US Centre for Medicaid Services (CMS) has defined tele-health as *"the use of telecommunications and information technology to provide access to health assessment, diagnosis, intervention, consultation, supervision and information across distance. Tele-health includes such technologies as telephones, facsimile machines, electronic mail systems, and remote patient monitoring devices, which are used to collect and transmit data for monitoring and interpretation"* (100). However, other organisations have different definitions. The US Health Resources and Services Administration (HRSA) has defined tele-health as *"the use of electronic information and telecommunications technologies to support long-distance clinical healthcare, patient and professional health-related education, public health and health administration"* (101). The California Health Care Foundation (CHCF) has described it as *"the mode of delivering healthcare services and public health via information and communication technologies to facilitate the diagnosis, consultation, treatment, education, care management and self-management of a patient's healthcare while the patient is at the originating site and the healthcare provider is at a distant site"* (102). Although every organisation has a different definition of tele-health, the conclusion is similar: it involves the integration of technology with clinical practice to support care at a distance.

1.3.1 History of tele-health

The idea of providing healthcare at distance was born in the early 1900s when the radio was invented (103). In 1924, Fibs predicted that *"Teledactyl"* would be

available by 1975 (a technological instrument that would allow the provision of healthcare services at a distance) (104). In 1964, the Nebraska Psychiatric Institute used television circuits to link with Norfolk State Hospital for consultation and education purposes (tele-medicine) (103). After that and due to economic inflation, the concept of tele-health was no longer a priority until the positive Norwegian experience from mid-1988 to the early 1990s of using tele-medicine in rural areas, in routine practice, which encouraged other countries to expand the use of tele-health (105). The use of tele-health after 2000 evolved as mobile phone ownership started to increase, which permitted text and call-based services. In 2006, smartphones were introduced to the market and phone applications were accessible. That helped advance tele-health services, which then became app-based (i.e. not limited to text and call) (106).

1.3.2 Tele-health types

According to the CHCF (102), tele-health can be classified into four models:

1- Live video (synchronous): real time interaction via telecommunication between clinician and patient.
2- Store and forward (asynchronous): the use of telecommunication to transfer a patient's records to another clinician (not real time) for consultation, second opinion, etc.
3- Mobile health (mHealth): is the use of mobile devices and apps to communicate with the patient for health purposes (education, management, care).
4- Remote Patient Monitoring (RPM): whereby patient data are being monitored and sent to a healthcare provider.

1.3.3 Tele-health in COPD

One of the keys to enhancing COPD patients' quality of life and lowering health-care costs is to better control the disease and improve patient self-management skills. Researchers worldwide have tried different approaches to achieving this goal, believing that predicting or permitting early detection of an exacerbation via tele-health may help lower the cost of COPD, start treatment earlier, better control the disease, assure faster recovery, and increase the patient's self-management. Exacerbation detection is most often achieved by monitoring symptoms; few studies have used physiology variables. This is despite exacerbations being associated with changes in physiological measurements in cardiovascular and respiratory systems (described later).

Successes in tele-health/tele-monitoring include sizeable decreases in healthcare cost for COPD patients, along with improved health outcomes. In 2013, De San Miguel et al. studied the cost benefit of tele-monitoring on the efficacy of reporting symptoms and physiological variables (107). While the findings are not statistically significant, it showed the potential of the tele-monitored group to have fewer emergency visits, fewer hospital admissions, and shorter hospital stays than the control group with standard support. Given this, annual cost savings were estimated to be $2,931 per person, even taking into account tele-monitoring equipment. Quality of life and patient satisfaction also increased as patients felt that they could more readily manage their own symptoms and exacerbations. De San Miguel et al. go as far to conclude that tele-monitoring is thus a cost-effective tool in COPD management and an efficacious intervention to increase patient self-monitoring and self-care. However, findings from this study should be interpreted

with caution as the study was under powered, and the hospitalisation rate at baseline was not collected, which questions if the difference in hospitalisation rate reported during the study was changed as a result of using tele-health or due to the patients' history. In a 2014 systematic review, the cost-effectiveness of tele-health with COPD was assessed, finding that tele-health services were cost-effective to the hospital and health care facilities (108). Even though in this review the findings showed the potential of cost-effectiveness of using tele-health with COPD patients, the economic quality of the studies included were poor, and the heterogeneity of the studies was not considered, which means that a more balanced view would be that the cost-effectiveness of tele-health remains unclear. A more recent clinical trial conducted in 2017 on 1225 COPD patients from 26 districts has a different conclusion. They reported that the use of tele-health with COPD would contribute to a total cost difference of €728/year/patient compared to usual care (109). Therefore, they concluded that tele-health would not be cost-effective. However, this was a clinical trial that included all types of COPD patients, and this could play a role in cost-effectiveness, as patients with mild COPD might have been seen or contacted unnecessarily. The organisations and health care providers that participated in this study underwent training and education sessions, which was an added cost of tele-health. The cost of education was not reported, thus it is not clear how much this had affected the reported cost difference.

Martin Lesende et al. (110) in 2013 investigated the implications of tele-monitoring on patients with chronic cardiorespiratory disease living at home (heart failure & chronic lung disease) in respect of the length of hospital stay and hospitalisation. Fifty-eight participants recruited from 20 health centres in Spain

(experimental group n= 28) participated for 12 months. Only 21 out of the 28 participants completed the study (chronic lung disease n= 8, COPD n= 6). Participants measured their blood pressure, heart rate, respiratory rate, oxygen saturation, body temperature and weight daily, and filled a health status questionnaire. Upon completion of the study, the researchers observed a significant reduction (p= 0.033) in all-cause hospitalisation, and a notable reduction in specific cause hospitalisation, length of hospital stay, and use of healthcare resources. The researchers reported that there were statistically significant changes in heart rate and oxygen saturation parameters five days preceding hospital admission in patients with chronic lung disease (p=0.003), and that in 94.3% of instances these were due to exacerbation. Lastly, Martin Lesende showed the total number of alerts generated from the system and defined those alerts as an indication of patients' vital signs exceeding the pre-set threshold limits.

Tele-monitoring has perhaps the greatest potential in the detection and monitoring of acute exacerbations of COPD, an important element in preventing mortality. Segrelles et al. (111) in 2014 studied two groups of COPD patients for seven months: one group was assigned to home tele-health monitoring (n= 30 patients), and the other group to conventional care monitoring (n= 30 patients. The researchers examined blood pressure, oxygen saturation, heart rate, and peak expiratory flow via monitoring devices connected to a respiratory service in a local hospital system. The monitoring device contained an exacerbation failsafe, which assessed the validity of a "*red flag exacerbation signature*", prior to notifying the respiratory specialist, which asked the patient several follow-up questions after detecting a possible COPD exacerbation. 80% of detected exacerbations were

discovered quickly in early or moderate stages and treated remotely in the patients' homes. The results showed a significant reduction in non-invasive ventilation (NIV) need (0 patient on telehealth vs 8 patients on conventional care, $p< 0.0001$) prior to hospitalisation, reduced emergency department (ER) visits (20 telehealth vs 57 control, $p= 0.001$), hospital admissions (12 telehealth vs 33 control, $p = 0.015$) and length of hospital stay (105 days telehealth vs 276 days control, $p= 0.018$), which reflected the success of tele-monitoring. However, the positive outcomes from this study could also be due to integration of tele-health with the scheduled regular visits of each patient with their care giver (primary/secondary care). Therefore, in this case the tele-health intervention could be considered as an add on service to usual care, unlike the previously mentioned studies.

In 2014 Fernandez-Granero et al. (112) contributed to the literature on tele-monitoring effectiveness for detecting exacerbations. A sample of 15 COPD patients underwent tele-monitoring for six months using a novel self-administered electronic daily questionnaire. The questionnaire comprised twelve variables. The results showed that 40 out of 41 exacerbations were detected utilising a tele-monitoring system in 4.8 ± 1.8 days with 88.3% accuracy. The researchers concluded that tele-monitoring had great potential to permit early detection of exacerbations to benefit patient health and economic efficacy. This study also had important limitations. Findings cannot be generalised due to the small sample size, and the exacerbation definition used in this study was based on Anthonisen criteria (changes in two major and/or minor symptoms for two consecutive days) whereas, in clinical practice, exacerbations are defined by changes in symptoms that result in taking extra medication.

Advances in technology have offered new routes in employing tele-health. In 2014, Williams et al. (113) validated the use of an mHealth application in tele-monitoring in 19 COPD patients. Utilising a downloadable application for tablets consisting of a platform which included a symptom diary, pulse oximetry, and self-management materials including images, videos, and text, Williams et al. noted from qualitative interviews that patient awareness of self-management and COPD variability improved. Patient data revealed a better likelihood of personal responsibility in COPD monitoring.

One of the challenges of tele-health using physiological parameters, and a criticism of all the above studies that we specifically address in this thesis, is the day-to-day variation in such measures. Clarke et al. (114) highlighted the importance of monitoring a dynamic threshold of daily oxygen saturation for the early detection of exacerbations. One study aim was to solve a critical issue with patient self-monitoring where single SpO_2% ratings resulted in low accuracy of exacerbation and a high rate of false alarms. To do this, they developed an algorithm which analysed the median and maximum of several daily measurements to develop a single representative value of a time series to increase the accuracy of the reading. Data were further analysed against the time series of multiple days' measurements. The proposed algorithm was able to detect trends in the oxygen saturation at an exacerbation, with significantly lower false alarms that could result in unnecessary treatment or hospitalisation. However, this approach ignored the fact that oxygen saturation and heart rate may also vary with other stimuli such as exercise, and new approaches were required, which our research is designed to address.

My Department had its own published pilot data in this field. Hurst et al. in 2010 (115) examined the ability to discern exacerbations from day-to-day fluctuations using domiciliary pulse oximetry, studying a cohort of 33 COPD patients to investigate the mechanism of exacerbation in relation to the onset of physical symptoms. They discovered that changes in heart rate and oxygen saturation analysed by domiciliary pulse oximetry, and combined with a composite score of other exacerbation variables, was capable of differentiating exacerbation occurrence from day-to-day COPD fluctuation (Figure 5). This has implications for the success of multiple physical variable analysis of COPD in tele-monitoring methods. However, one-off readings of heart rate and saturation may still be affected by non-COPD related factors, such as exercise and anxiety.

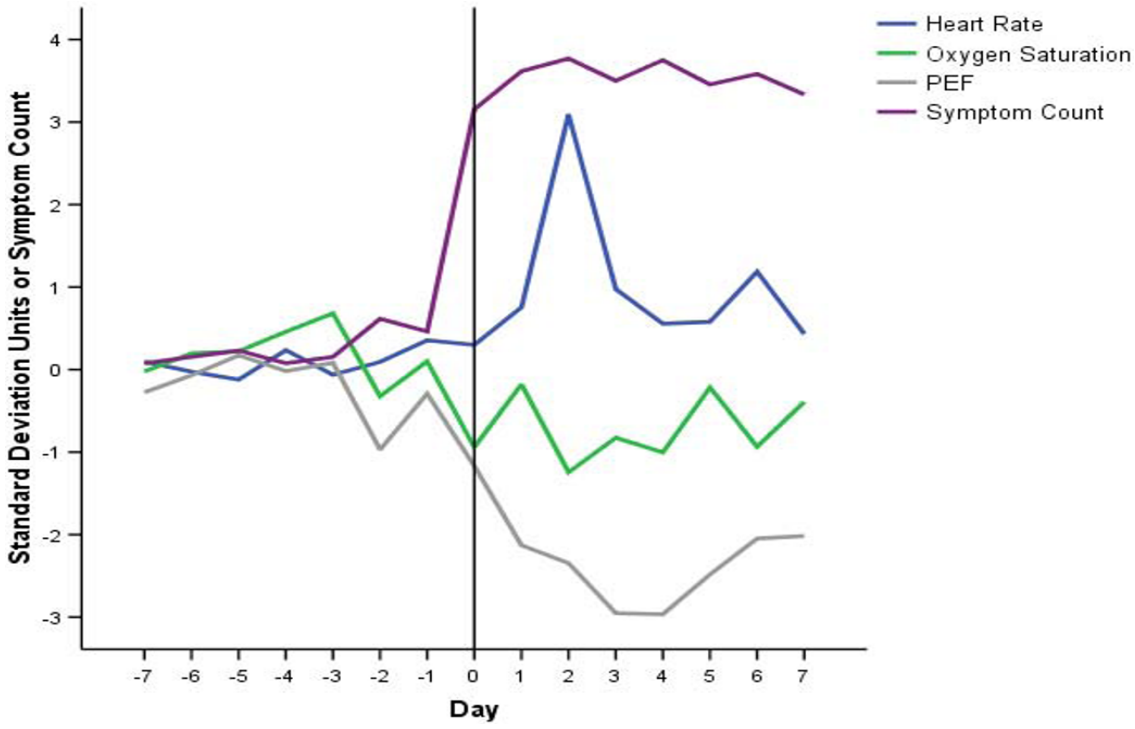

Figure 5. Time course of symptoms and oximetry variables (heart rate and oxygen saturation) at exacerbation (63). The Y-axis represents the amount of change in SD from variables' baselines (Z score). The X-axis represents the monitoring period: pre exacerbation= day -7 to day -1, exacerbation onset as noticed by the patient = day 0, and post exacerbation= day 1 to day 7.

In 2015, Borel et al. (116) observed 44 patients for six months being managed with domiciliary non-invasive ventilation (NIV) and oxygen therapy. In this study, the researcher confirmed that monitoring physiological parameters could help in the detection of an exacerbation. Borel detected 21 exacerbation events by monitoring respiratory rate (RR), percentage of respiratory cycles triggered by the patient (%trigg), and NIV usage, coupled with a daily EXACT-PRO questionnaire. Readings were considered abnormal if > 75% (high value) or < 25% (low value). Exacerbation was defined as an abnormal respiratory rate and %Trigg ≥ two days, or ≥ three days of abnormal daily usage of NIV. Borel et al. found that when the self-reported questionnaire data was analysed alongside RR, %Trigg, and rate of NIV usage, the rate of successful exacerbation detection increased linearly.

In 2015, Mohktar et al. (117) validated the usefulness of physiological tele-monitoring in predicting COPD exacerbations. In their study, Mohktar et al. tested an algorithm which analysed forced expiratory volume in 1s, heart rate, respiratory rate, blood pressure, body-temperature, body weight, and oxygen saturation, alongside questionnaires. They found that classification of the physiological and symptoms variables was highly effective in predicting 55/90 exacerbations at 71.8% accuracy, 80.4% specificity and 61.1% sensitivity. The study showed the ability to combine symptoms and physiological parameters to improve the decision support system.

In summary, challenges remain in tele-health based assessment of physiological measurements to detect COPD exacerbations. Notably, one-off readings are variable and may depend on patient activity, medication, and states such as anxiety. **It is in this context that the current research addresses a**

completely novel hypothesis: that domiciliary overnight monitoring of physiological variables can permit reliable early detection of COPD exacerbations without unwanted effects on physiology from, for example, anxiety, medication and exercise.

2 Hypotheses and Aims

Systematic review of the existing literature (see Chapter 3) enabled me to formulate specific hypotheses. Each hypothesis was then tested, and is presented here as a separate chapter. Therefore, the overall hypotheses and aims for this thesis are:

Study 1: Monitoring of Physiological Parameters to Predict Exacerbations of COPD: A Systematic Review

Hypothesis: Existing data will support use of physiological variables to facilitate the earlier detection of COPD exacerbations.

Aim: To summarise and report the existing literature on the value of domiciliary physiological monitoring in predicting exacerbations in patients with COPD.

Study 2: Patient specific parameter thresholding to support domiciliary monitoring in COPD

Hypothesis: Alarm limits set for individual patients (personalised threshold) based on an assessment of their own baseline data can reduce the rate of 'false alarms'.

Aim: To show the benefit of setting patient specific parameters in tele-health monitoring compared to the use of arbitrary limits. Specifically, to show that patient specific alarms would reduce unnecessary calls.

Study 3: Predicting Hospitalisation due to COPD Exacerbation using data from Home Non-Invasive Ventilation modems.

Hypothesis: Data extracted from remotely-monitored home NIV machines can predict a COPD exacerbation resulting in hospital admission.

Aim: To study the value of using data obtained from home NIV devices in clinical practice to predict exacerbations of COPD that result in hospitalisation.

Study 4: Use, Utility and Methods of Tele-Health for COPD Patients: National and International Surveys

Hypothesis: That there will be wide-spread use of tele-health in COPD, without a strong evidence base in which healthcare providers have no clear guidelines on how to specify the alarm limits for each patient.

Aim: To summarise and explore the use and techniques that have been used by healthcare providers for telehealth in COPD, and specifically how to personalise alarm limits for each individual.

Study 5: Continuous Overnight Monitoring to Predict Exacerbations of COPD

Hypothesis: Domiciliary overnight monitoring of physiological variables can permit earlier detection of COPD exacerbations than both once daily monitoring, and detection by the patient.

Aim: To study the possibility of predicting a COPD exacerbation by monitoring patients' physiological parameters overnight, thus removing non-COPD related effects, for example, anxiety and exercise on the physiological signal.

Study 6: Patients' Acceptance of Overnight Continuous Pulse-Oximetry Monitoring

Hypothesis: That the level of acceptance of continuous overnight monitoring may vary due with patient characteristics, but that overall the patient would find this technique acceptable.

Aim: To evaluate patients' acceptance of continuous overnight home pulse-oximetry monitoring.

3 Systematic review

Monitoring of Physiological Parameters to Predict Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): A Systematic Review

A general introduction has been given above. In completing my literature review it became apparent that there were no existing systematic reviews of the role of domiciliary monitoring to predict COPD exacerbations. Therefore, in addition to being necessary background to my PhD, we went on to publish this systematic review(118) (Appendix 8).

3.1 Aim

To summarise and report the existing literature on the value of domiciliary physiological monitoring in predicting exacerbations in patients with COPD.

3.2 Methods

Search Strategy

This systematic review (PROSPERO registration CRD42016046643) was compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (119). The original search was completed up to April 6, 2016, and updated for this thesis in 2018. The search was performed in the Medical Literature Analysis and Retrieval System Online, or MEDLARS Online (Medline), Excerpta Medica dataBASE (Embase), Allied and Complementary Medicine Database (AMED), Cumulative Index of Nursing and Allied Health Literature (CINAHL), and the Cochrane clinical trials database. The search terms used are detailed in Appendix 1, Table A1 and Table A2. In addition to the electronic database search, the reference list of eligible articles was also screened.

Inclusion Criteria

The studies included in this review met the following criteria: (1) Stable COPD; (2) Domiciliary monitoring; (3) Monitoring any physiological variables; (4) Reporting statistical analysis of the measured physiological variables; (5) Prediction of exacerbations via physiological variables.

Exclusion Criteria

We excluded the following: (1) Books; (2) Systematic reviews; (3) Non-English manuscripts; (4) Conference abstracts with no full-text; (5) Non-full text articles.

The main outcome of interest was variation in physiological parameters before and during COPD exacerbations, and the ability to measure changes in physiological variables to provide early detection of COPD exacerbations.

Data Collection

Screening of the titles and abstracts was performed to eliminate all non-relevant studies. Potentially relevant titles and abstracts were read in full-text to evaluate if they were eligible or not. In addition to screening and evaluating for eligibility, the reference list of the eligible articles was screened. The eligibility of the included studies was confirmed by Professor Hurst. Disagreement on five studies was resolved after discussion.

Quality Assessment

Quality assessment of the included studies was performed by each author individually-based on two different modified scales, the Cochrane tool (120) and the Newcastle-Ottawa scale (121). The Cochrane quality assessment tool consists of

seven questions to evaluate randomised studies included in this review. The Newcastle-Ottawa scale consists of seven questions used to assess cohort and non-randomised studies included in this review. The assessment was performed by each author individually, and any disagreement was solved by discussion.

Synthesis of Results

The primary purpose of this systematic review was to assess the feasibility of predicting COPD exacerbations by domiciliary monitoring of physiological parameters. Because of significant methodological heterogeneity between included studies, meta-analysis was not attempted. However, a narrative synthesis of the results of the studies was performed, and full details of the included studies are reported in Table 3, and the definitions of exacerbation used are reported in Table 4.

Table 3. Detailed description of the 16 included studies.

Author	Subjects and COPD Severity	Country	Measures	Quality	Detailed Description	Results
Seemungal et al., 2000 (122)	N = 101 severe COPD	United Kingdom	PEFR FEV_1 Symptoms	Moderate quality	**Period:** 2.5 years. PEFR and symptoms measured daily, post morning medication. In a subgroup of 34, FEV_1 was measured	Analysis of 504 exacerbations: Lung function changed significantly on the day of onset ($p < 0.001$). A decrease in the median of: PEFR by 8.6 L/m FEV_1: 24.0 mL FVC: 76.0 mL
Cooper et al., 2009 (123)	N = 19 mild−severe COPD	United Kingdom	HR SpO_2% PEFR FEV_1 Symptoms	High risk of bias	**Period:** 4 months. Participants measured their vital signs and recorded their symptoms twice a week in the morning	Analysis of four exacerbations: Concluded that SpO_2% was the variable most closely associated with exacerbation but no statistical significance reported
Sund et al., 2009 (124)	N = 18 severe COPD	United Kingdom	FEV_1 Symptoms	Low quality	**Period:** 6 months. Daily electronic diary and three spirometry manoeuvres performed, daily in the evening	Analysis of 75 exacerbations: 55 exacerbations were detected via tele-health (symptoms) and 6/55 exacerbations were detected via FEV_1 alone (p = not significant). Exacerbation detected via FEV_1 was defined as a 10% fall in FEV_1 for ≥2 consecutive days.

Hurst et al., 2010 (115)	N = 31 severe COPD	United Kingdom	HR SpO_2% PEFR Symptoms	Moderate quality	**Period:** 9 months. Daily paper diary cards	Analysis of 13 exacerbations: Variation was noted prior and during the onset of exacerbation in PEFR, HR, and SpO_2%. Maximal change in SpO_2% and HR occurred two days into exacerbation: SpO_2% had fallen by −1.24 SD, HR increased by +3.09 SD. Maximal change in PEFR occurred four days into exacerbation: −2.97SD Composite Score to detect exacerbation: AUC = 0.832, $p < 0.05$.
Jensen et al. in 2012 (125)	N = 57 moderate−severe COPD	Denmark	HR SpO_2% BP	Moderate quality	**Period:** 4 months. Daily diary cards	Analysis of 9 exacerbations: Their algorithm classified variables into 273 features and was able to detect seven exacerbations via vital signs with 70% sensitivity, 95% specificity, AUC = 0.73.
Berge et al., 2012 (126)	N = 137 severe COPD	Netherlands	Salbutamol use PEFR Symptoms	Moderate quality	**Period:** 15 months. Daily diary cards	Analysis of 101 exacerbations: Significant decrease in PEFR 15 L/min at exacerbation compared to baseline.

Yanez et al. in 2012 (127)	N = 89 severe COPD (On O_2 therapy)	Spain	Respiratory Rate (RR)	Moderate quality	**Period:** 3 months. Daily monitoring of respiratory rate, using a sensor inserted into the domiciliary oxygen supply system	Analysis of 10 exacerbations: Increase in the mean respiratory rate in 21/30 exacerbations, 1–5 days prior to hospitalisation Mean of respiratory rate raised: Five days: 15.2 ± 4.3 min^{-1} to 19.1 ± 5.9 min^{-1} Two days: 2.3 min^{-1} (15% from baseline) One day: 4.4 min^{-1} (30% from baseline) All p-value < 0.05
Martin Lesende et al. 2013 (110)	N = 58 Heart failure (27.6%) + O_2 therapy (57.1%) + moderate−very severe COPD and asthma (25.9%)	Spain	HR SpO_2% BP RR Weight Temperature Symptoms	High risk of bias	**Period:** 12 months. Daily monitoring	In the five days preceding hospital admission: Mean SpO_2% fell from 93.1% to 91.0% (4.6 SD), and mean HR increased from 77.8 to 84.2 min^{-1} (17.1 SD) p = 0.003 for both. No significant change for respiratory rate, body temperature and blood pressure.
Pedone et al. 2013 (128)	N = 99 moderate−severe COPD	Italy	HR SpO_2% Temperature Physical activity	High risk of bias	**Period:** 9 months. Automatic recording of vital signs, a mean of four times per day.	Analysis of 13 exacerbations: SpO_2% fell three days before an exacerbation, which permitted timely intervention, and was associated with a 33% reduction in hospitalisation rate (p = not shown, data displayed in a Figure only).
Segrelles et al., 2014 (111)	N = 60 severe COPD (On O_2 therapy)	Spain	HR SpO_2% BP PEFR	High risk of bias	**Period:** 7 months. Participants monitored their vital signs every morning, but PEFR was three times/week.	Analysis of 50 red flags: confirmed red flag defined as moderate, severe or very severe exacerbation. Tele-health was associated with significant reduction in acute NIV usage (p < 0.0001), ER visits (p = 0.001), admissions (p = 0.015) and bed days (p = 0.018). Reported that SpO_2% and PEFR were the most predictive parameters (but data not reported).

Harding et al., 2015 (129)	N = 18 moderate−very severe COPD	United Kingdom	HR SpO_2% Symptoms	Moderate quality	**Period:** 6 months. Each participant asked to fill a daily symptom diary card.	Analysis of 37 exacerbations: 15/37 exacerbations were identified three days prior to medication self-initiation. Alerts related to events: 47 symptom alerts (16 patients) 80 HR alerts (18 patients), and 62 SpO_2% alerts (17 patients). p = not shown.
Mohktar et al., 2015 (117)	N = 21 moderate−very severe COPD	Australia	HR SpO_2% BP RR Weight Temperature FEV_1 Symptoms	Moderate quality	**Period:** 11 months. Participants daily monitored their vital signs and symptoms	Analysis of 90 exacerbations: The designed algorithm identified 55/90 true exacerbations (71.8% sensitivity 80.4% specificity). FEV_1 value (k = 0.21), mean of distribution of SpO_2% (k = 0.27) and the weight (k = 0.21) were the most predictive variables (p = not shown).
Fernandez-Granero et al., 2015 (130)	N = 16 severe−moderate COPD	Spain	Respiratory sound	Moderate quality	**Period:** 6 months. Daily recorded respiratory sounds using a microphone over the super-sternal notch	Analysis of 33 exacerbations: 25 out of 33 exacerbations were detected 5 ± 1.9 days prior to the onset of exacerbation by changes in sounds (p = not shown).
Burton et al., 2015 (131)	N = 33 mild−very severe COPD	United Kingdom	HR SpO_2% FEV_1 PEFR Symptoms	Moderate quality	**Period:** >200 days. Each participant asked to fill a symptom questionnaire, and measure heart rate, and SpO_2% daily. FEV_1 and PEFR monitored weekly.	Analysis of 172 exacerbations: Increase in HR (87 min^{-1}–94 min^{-1}) at the onset of exacerbation and mean SpO_2% fell (93.6% to 92.4%) around the onset of exacerbation. Exacerbation associated with a reduction of 0.1 L in FEV_1.
Borel et al., 2015 (116)	N = 44 severe COPD (On NIV and O_2 therapy)	France	RR %Triggering NIV usage Questionnaire	Moderate quality	**Period:** 6 months. Daily monitoring via the ventilator and daily EXACT-Pro questionnaire.	Analysis of 21 exacerbations: 21 exacerbations detected, and the risk of exacerbation was high if high value noted on ≥ two days out of five for RR P = 0.01, and %Triggered Breaths p = 0.037, but not total NIV usage p = 0.097).

Hamad et al., 2016 (132)	N = 183 COPD *	United Kingdom	HR SpO_2% Temperature Physical activity Symptoms	Moderate quality	**Period:** 4 months. Daily monitoring.	Analysis of 98 exacerbations: 80/98 showed changes on one or more tele-health parameters prior to hospitalisation/exacerbation onset. 30 exacerbations resulted in hospitalisation and 7/30 had significant SpO_2% reduction (significant defined for each patient individually, $p = 0.049$) 12/98 exacerbations had a significant SpO_2% fall ($p < 0.05$).

* Disease severity not reported. COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; PEFR: peak expiratory flow rate; FEV_1 forced expiratory volume in one second; HR: heart rate; SpO_2%: peripheral capillary oxygen saturation; BP: blood pressure; RR: respiratory rate; NIV: non-invasive ventilation; EXACT: Exacerbation of Chronic Pulmonary Disease Tool; Pro: Patient-reported outcome; SD: standard deviation; AUC: area under the curve.

Table 4. Detailed description of the 16 included studies: definition of exacerbation.

Author	Definition of Exacerbation
Seemungal et al., 2000 (122)	Anthonisen criteria (62).
Cooper et al., 2009 (123)	Not explained.
Sund et al., 2009 (124)	Increase of two symptoms and/or ≥10% reduction of FEV_1 for ≥2 consecutive days; or the use of antibiotics and/or prednisolone.
Hurst et al., 2010 (115)	≥2 of new or worsening symptoms (one should be increased breathlessness, sputum volume of sputum purulence) for ≥2 days.
Jensen et al. in 2012 (125)	Admission to hospital, or started antibiotics or steroids with specific symptoms.
Berge et al., 2012 (126)	Not explained.
Yanez et al., 2012 (127)	Clinical diagnosis by an emergency room clinician.
Martin Lesende et al., 2013 (110)	Not explained.
Pedone et al., 2013 (128)	Change in symptoms that lead to a change in medication.
Segrelles et al., 2014 (111)	GOLD definition.
Harding et al., 2015 (129)	Initiation of antibiotics or steroids or both.
Mohktar et al., 2015 (117)	GOLD definition.
Fernandez-Granero et al., 2015 (130)	Use of medication for exacerbation, and/or unplanned emergency room visits and/or hospital admissions.

Burton et al., 2015 (131)	Anthonisen criteria (62), or started antibiotics.
Borel et al., 2015 (116)	If abnormal values of respiratory rate and % triggered breaths were reported for two days or more, or abnormal values of NIV daily usage were reported for three days or more out of five. Abnormal values were defined as “value of a parameter was >75th or <25th percentile, the day was recorded as abnormal value’ (‘high value’ > 75th, ‘low value’ < 25th).
Hamad et al., 2016 (132)	Admission to hospital, or started antibiotics or/and steroids.

3.3 Results

The systematic review search generated 3377 articles, 345 were excluded due to duplication. After screening the titles and abstracts, 28 articles out of 3032 were potentially relevant to the inclusion criteria. After that, full-text screening of the 28 articles was conducted to assess eligibility, which resulted in 13 relevant articles. The reference list of the relevant articles was also examined which resulted in identification of three further articles giving 16 in total (Figure 6).

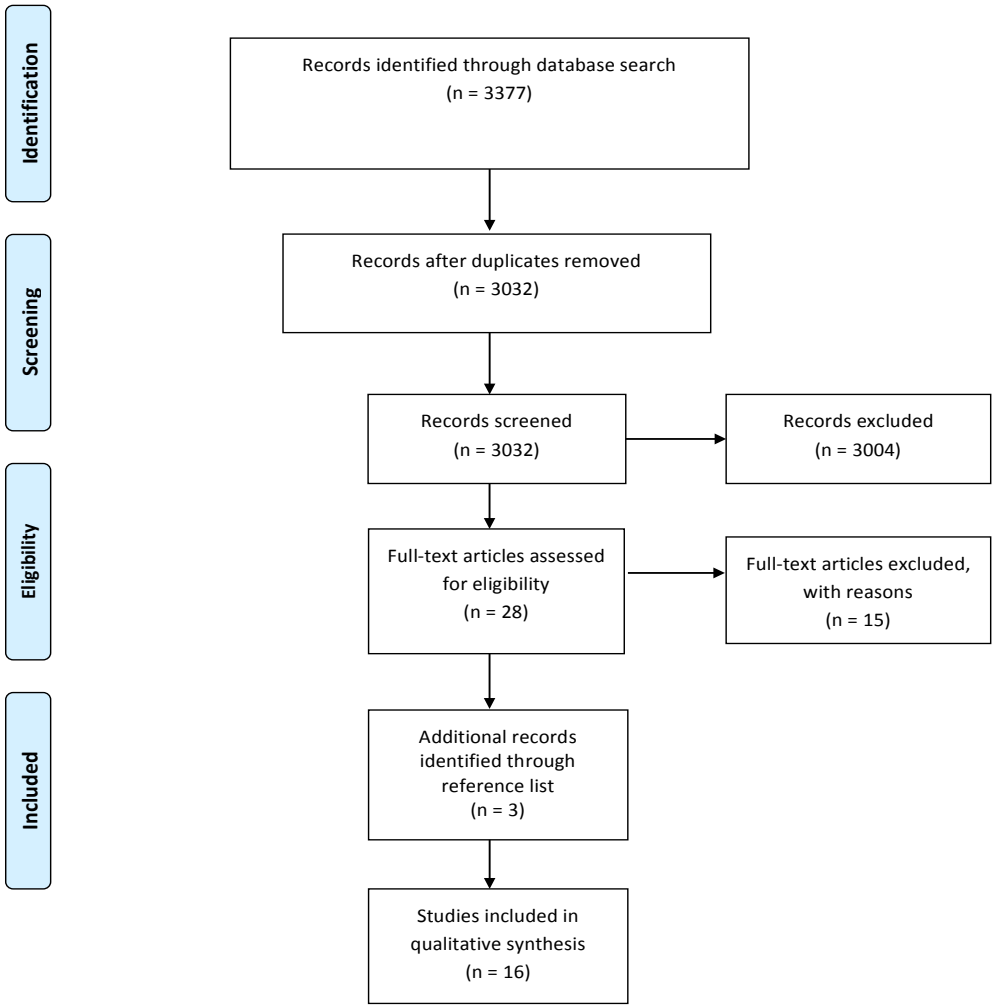

Figure 6. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram.

Of the 16 articles that met the pre-specified inclusion criteria, all the studies were conducted prospectively, and in seven different countries: one each in Australia, Denmark, France, Italy, Netherlands, four in Spain, and seven in the United Kingdom. Most of the articles were published in 2015 (5/16), with three in 2012, two each in 2009 and 2013, and one each was published in 2000, 2010, 2014 and 2016. The duration of the studies varied from three months to fifteen months except for one study, which was run for 30 months. The sample size varied from 16 to 183 participants (eight studies <50 patients, five studies ≥50 patients, and three studies >100 patients). Fifteen studies were on COPD patients only (at different disease stages), and one was on heart failure and chronic lung disease patients (126).

3.3.1 Quality Assessment

Among the 16 identified articles, four studies were randomised clinical trials and 12 were cohort studies. The four studies evaluated using the modified Cochrane risk of bias tool (120) were ranked as being at high risk of bias. The 12 studies evaluated by the modified Newcastle-Ottawa scale (121) were all ranked as moderate quality except for one, which was ranked as low quality.

3.3.1 Monitoring Vital Signs to Predict Exacerbation

Heart Rate and Oxygen Saturation

Most of the included studies - 14/16 - monitored the participant's vital signs and assessed the capability of vital signs to predict COPD exacerbation. Although heart rate (HR) and oxygen saturation (SpO_2%) were monitored in 10/16 studies (110, 111, 115, 117, 123, 125, 128, 129, 131, 132), 7/10 studies did not report any statistical analysis for the HR and SpO_2% variation. However, they concluded with

the possibility that heart rate and/or SpO_2% may be useful in detecting deterioration. Four studies (three at moderate quality, and one at high risk of bias) reported a significant variation ($p \leq 0.05$) in HR and/or SpO_2% prior to the onset of COPD exacerbation (110, 115, 131, 132). In Hurst et al. (115), the magnitude of the fall in SpO_2% two days into the exacerbation was −1.24 standard deviation (SD) and the rise in HR was +3.09 SD above the patient's baseline. Martin-Lesende et al. (110) reported the difference between the mean values monitored over the whole study period, which were for SpO_2% 93.1% (2.2 SD), and for HR 77.8 min^{-1} (14.6 SD); Moreover, the mean values monitored over the five days prior to cause-specific admission were SpO_2%, 91.0% (4.6 SD) and HR, 84.2 min^{-1} (17.1 SD), $p = 0.003$ for both. There was therefore a typical rise in HR of 7 min^{-1} and fall in SpO_2% of 2% (similar to the data by Hurst in absolute magnitude). Burton et al. (131) reported that the magnitude of SpO_2% fall and HR rise was approximately 1 SD (SpO_2% fall from 93.6% to 92.4%, and HR increased from 87.4 min^{-1} to 93.7 min^{-1}).

Respiratory Rate

The works of Yanez and Borel, which were ranked as moderate quality (116, 127), evaluated variations in respiratory rate prior to an exacerbation. In both, the change was statistically significant ($p \leq 0.05$). Importantly Yanez et al. reported an increase in the mean respiratory rate one to five days prior to hospitalisation due to an acute exacerbation. At 48 hours, the mean respiratory rate increased by 2.3 min^{-1} (15% from baseline) with 72% sensitivity and 77% specificity (area under the curve (AUC) = 0.76, $p < 0.05$) for detecting exacerbation, whilst the rise noted 24 h prior to hospitalisation at 4.4 min^{-1} (30% from baseline) had a 66% sensitivity and 93% specificity (AUC = 0.79, $p < 0.05$) for exacerbation detection. At five days

before hospitalisation, the mean respiratory rate rose from 15.2 ± 4.3 min^{-1} to 19.1 ± 5.9 min^{-1} ($p < 0.05$) suggesting a longer window for preventing hospitalisation. However, in contrast, Martin Lesende (110) did not see significant change in the respiratory rate five days before hospitalisation. Mohktar (117) included respiratory rate with daily monitored variables, but no analysis was reported.

Blood Pressure and Temperature

Four studies of 16 (two at high risk of bias and two at moderate quality) included blood pressure monitoring (110, 111, 117, 125), but there was no evidence indicating changes in blood pressure as a variable with high predictive capacity for exacerbation (p-value not significant). Likewise, body-temperature was monitored in 4 out of 16 studies. Martin-Lesende (110) compared the mean temperature in the overall follow-up period, 35.9 °C (0.4SD), to the mean of five days, 35.5 °C (1.0 SD), prior to cause-specific admission. Changes in body temperature resulted in 27.8% of alerts (only 5.6% of alerts were due to an increased temperature over 37.0 °C). Hamad (132) reported increased body-temperature in just 9 out of 98 exacerbations.

Five studies (two at high risk of bias and three at moderate quality) out of 16 (123, 125, 128-130) did not provide sufficient statistical analysis of changes in vital signs despite reporting these variables. For example, Pedone (128) evaluated the capability of a tele-monitoring system for lower hospitalisation rates, and to identify COPD exacerbation onset. The researchers did not report whether the result was statistically significant, but noted a 33% reduction in the risk of hospitalisation. Pedone also noted a fall in SpO_2% in the three days preceding the onset of an

exacerbation, which therefore led to prediction of COPD exacerbation. Furthermore, Jensen (125) tried to develop an algorithm to enhance the prediction of COPD exacerbations. The four variables of heart rate, systolic blood pressure, diastolic blood pressure, and oxygen saturation were monitored and classified into 273 features. Jensen reported that their system was able to distinguish ten COPD exacerbations with 70% sensitivity, 95% specificity, and 0.73 AUC.

Considered together, SpO_2% was the most studied variable before an exacerbation episode, and the variable which has been reported to have the highest predictive capacity, although the magnitude of change is typically small (1%–2%) – perhaps too small to be clinically useful.

3.3.2 Monitoring Lung Function to Predict Exacerbations

Lung function, particularly spirometry, is a valuable test for diagnosing COPD and evaluating disease progression. A few studies assessed the usefulness of lung function variables in predicting acute exacerbation. Eight studies (two at high risk of bias, one at low quality, and two at moderate quality) of 16 (111, 115, 117, 122-124, 126, 131) monitored either the peak expiratory flow rate (PEFR), or the forced expiratory volume in one second (FEV_1), or both. Three studies (122, 123, 131) measured FEV_1 and PEFR at different frequencies (per day/per week). Seemungal et al. (122) reported data from 101 COPD patients, PEFR, FEV_1 and vital capacity (FVC) on the day of exacerbation onset showed significant changes ($p < 0.001$). This analysis of 504 COPD exacerbations revealed a fall in the median PEFR of 8.6 (interquartile range (IQR) 0 to 22.9) L/min, FVC of 76.0 (IQR −40.4 to 216.4) mL, and FEV_1 of 24.0 (IQR −16.1 to 84.3) mL. Burton et al. (131) reported a strong

correlation between FEV_1 and PEFR changes, and a 0.1 L reduction in FEV_1 was associated with a change in the symptom score.

Sund et al. at low quality and Mohktar et al. at moderate quality (117, 124) focused only on FEV_1. Sund (124) detected 55/75 exacerbations using monitoring, and 6/55 exacerbations were detected only via FEV_1 (defined as a 10% fall in FEV_1 for ≥2 consecutive days). Three studies (111, 115, 126) examined predicting COPD exacerbations with daily monitoring of PEFR. Segrelles (111) did not report detailed PEFR data, but reported that PEFR and SpO_2% were the most predictive variables. Hurst (115) reported a statistically significant reduction in PEFR before and during an acute exacerbation with a maximal −2.97 SD fall in PEFR four days into the exacerbation. Berge (126) reported a significant decrease in the mean of PEFR during an exacerbation episode, which was back to baseline in two weeks.

3.3.3 Monitoring Respiratory Sounds to Predict Exacerbations

In 2015, Fernandez-Granero at moderate quality (130) reported a study demonstrating that 25 out of 33 COPD exacerbations could be detected via monitoring patients' respiratory sounds at home. Each participant was asked to record his/her respiratory sounds daily by placing a microphone on the suprasternal notch. Exacerbation episodes were detected 5 ± 1.9 days prior to the exacerbation onset, with a sensitivity of 73.76% and 97.67% specificity.

3.3.4 Methodological Considerations

Alarm limits

A challenge in COPD is the variation between patients and how to set alarm limits for an individual patient because of day-to-day variation in physiological

parameters. Of the 16 articles included in this review, only eight studies (three at high risk of bias, one at low quality and two at moderate quality) (110, 115, 117, 123, 124, 128, 129, 132) mentioned that they had customised the alarm limits for each individual. Methods used were reported in six out of the eight studies. Cooper (123) monitored the participants for two weeks to identify the normal range for each to personalise the alert limits. Sund (124) set a baseline for each participant by taking the median and the mean after monitoring symptoms and FEV_1 for 14 days (exacerbation-free). In the Hurst study (115), heart rate, oxygen saturation, and peak expiratory flow rate were assessed for 30 days (symptom-free). These established a baseline of the selected variables with ±SD (Z scores). Pedone (128) customised the limits based on the participant's "clinical situation". Harding (129) personalised each participant's limits by applying a probability density function after monitoring the participant for six weeks, or having 40 sets of recorded daily data. Mokhtar (117) personalised the limits range in a different way; they took the median (50th percentile), lower (25th percentile), and upper (75th percentile). They then adjusted the lower limits to be 25th percentile minus 1.5 times the interquartile, and the upper limits to be 75th percentile plus 1.5 times the interquartile. There are no studies comparing different methods of personalising alarm limits.

Monitoring Characteristics

The approach pursued by the 16 studies to monitoring physiological signs was heterogeneous with regard to the type of equipment or instrument used to monitor and assess the participant's data. In some studies, a mobile/tablet app was used to communicate with the participant (128, 129), and transfer data. Some studies set up a monitoring station for each individual with different devices (110, 111, 116, 117,

123-125, 127, 128, 130-132), where the data were transmitted automatically through an internet modem. If a red flag was raised or threshold breached, a notification alert was sent to the system operator in real time. In two studies, an alternative form of monitoring was used. A diary card for symptoms and vitals was provided to participants, and a visit was arranged to collect the data (115, 122, 126).

Intermittent vs. Continuous Monitoring

In the reviewed articles, 16 studies monitored the participants' physiological parameters and symptoms intermittently. The frequency of monitoring/recording was varied, some once daily or multiple times daily. However, in four studies (123, 124, 131, 133), participant's data were monitored less than daily (different frequencies per week). In addition to that, sometimes measurements were restricted to mornings; however, in Harding et al. (129), the stipulated time for measurement recording was based on the patient's preference.

3.4 Discussion

This is the first systematic review examining the utility of monitoring physiological variables to predict exacerbations of COPD. In general, and as discussed below, the studies are small and heterogeneous, using different variables and different protocols. The need for better healthcare solutions in people diagnosed with chronic diseases is real. COPD imposes burdens on individuals and health care organisations. Whilst the methods hold promise, further adequately-powered studies are required to properly define the utility of physiological monitoring to predict exacerbations.

In this systematic review, compliant with PRISMA sixteen articles met the inclusion criteria. Five studies out of 16 (123, 125, 128-130) did not provide sufficient statistical data to draw conclusions consistent with the results of other studies, despite reporting changes in physiological variables (no p-values). The methodological quality of the studies was variable but generally low with 12 cohort studies ranked as moderate or low quality, and four trials ranked as having a high risk of bias.

We have described those studies that showed results in predicting/detecting an exacerbation episode via monitoring of physiological parameters. Since completion of the original search, an update in October 2018 identified one further study (134). This study was conducted by Milkowska-Dymanowska et al. in Poland on 19 severe to very severe COPD patients. Four variables (HR, SpO_2%, BP, and temperature) were monitored daily until the patient exacerbated. They reported that SpO_2% was the only variable that changed significantly, seven days prior to exacerbation with an estimate drop of 2% compared to the stable period (92.6% vs 90.8%, p= 0.007). Although this approach appears to be promising, further well-designed clinical trials are required to investigate the true magnitude and time-course, pre, during, and post an exacerbation episode, of changes in physiological parameters. Understanding the extent of the magnitude of change for each variable is critical in using this knowledge for early exacerbation detection. In three studies (110, 115, 131), the magnitude of the change in heart rate and SpO_2% reported was an increase of around 5 min^{-1} for heart rate and a fall of 1%–2% for SpO_2%. Two studies (116, 127) reported an increase in the respiratory rate before the onset of COPD exacerbation/hospitalisation. These findings all support the hypothesis that

monitoring of vital signs can detect respiratory deterioration, although the changes are small in magnitude. However, the question arises as to whether these variables can be reliable enough. Moreover, to answer that question we need to better understand the relationship between physiological signs and exacerbation symptoms. This has been examined in some of the above-mentioned studies (115, 122, 124). Hurst (115) combined peak expiratory flow (PEF) with a symptom score to provide optimal exacerbation detection.

Having demonstrated that monitoring physiological variables has the theoretical potential to detect COPD exacerbations, the second step is implementation of this in a clinical environment—tele-monitoring. To enable healthcare providers and patients to feel secure managing COPD and detecting acute exacerbations with no anticipated harm, an intelligent interface to provide live communication is essential. In the above-mentioned studies, various designs were employed. However, the optimal technique/algorithm requires more investigation. Despite the fact that tele-health offers the possibility for the clinician and the patient to be connected and monitored in a ‘virtual clinic’, the accuracy and specificity of this discipline are still uncertain. Developing an algorithm to detect an exacerbation is important because that would facilitate the services provided via tele-health. A particular challenge is around alarm thresholds. To increase the value of tele-health in self-management, a customised threshold for each patient is essential as this may help to decrease false alarms (see later Chapter 4), and differentiate between true deterioration and day-to-day variation. Six studies addressed this issue by specifying the alarm settings for each individual (115, 117, 123, 124, 128, 129), but using

different methods, such that the optimal way to set individual patient alarms remains an open question.

Even though most of the reviewed studies exhibited some significant positive results in the efficacy of physiological parameters in predicting/detecting COPD exacerbation, there are insufficient data to draw a secure conclusion in this review. This is due to the diversity of the designs, methods, and sample size of studies. The demand for technology to meet the needs of the COPD patient and society are increasing. Further clinical trials are therefore needed to achieve this.

Strength and Limitations

In this systematic review, a number of limitations can be considered. First, non-English studies (abstract and full text) were excluded. Second, only one author performed the screening of titles and abstracts, which may have increased the risk that studies were excluded inappropriately. Third, the definitions of exacerbation vary across the studies, which can make comparison between studies challenging. Fourthly, unpublished negative or positive studies cannot be captured and there is the potential risk of publication bias (over-representation of positive studies). The major strength of this study is that, to our knowledge, no pre-existing review has been conducted regarding the usefulness of monitoring physiological signs to predict COPD exacerbation.

3.5 Conclusions

The monitoring of physiological parameters may be useful in assisting earlier detection of COPD exacerbations, but further robust studies are required to confirm

this. A particular challenge is how to set alarm limits for individual patients given the heterogeneity inherent in COPD and COPD exacerbations.

In the next Chapter we will start to explore the utility of tele-health data in COPD by considering two local NHS services that are trialling tele-health applications, and specifically consider the role of personalised alarm limits.

4 Clinical pilot data

4.1 Tele-Health data "Patient specific parameter thresholding to support domiciliary monitoring in COPD".

In this chapter, I accessed data from an NHS pilot tele-health programme to explore if personalising patient alarm limits affected the number of alarms generated compared to standardised limits. These results were presented as an abstract at the European Respiratory Society congress (135) (Appendix 9).

4.1.1 Aim

To assess the benefit of setting patient-specific parameters in tele-health monitoring compared to the use of arbitrary alarm limits. Specifically, to show that patient specific alarms would reduce unnecessary calls.

4.1.2 Method

In this pilot analysis, we used data being collected from 10 COPD patients being collected in a domiciliary telehealth project following pulmonary rehabilitation, which is part of a clinical service delivered by Central and North West London NHS Foundation Trust (CNWL). Participants were prospectively invited to participate in the CNWL tele-health program in order to increase self-management post-pulmonary rehabilitation. Each participant was equipped with a tele-health interface device station that sends the patient measures and responds automatically. The patient's status was assessed every morning. Participants were instructed and trained to answer five respiratory questions, and take measurements of blood pressure, heart rate, oxygen saturation, and temperature. Participants were

asked to take the measurements once every day for five days per week. The Joint Governance Committee of CNWL approved the project as a clinical service development, and all participants consented for sharing their data for the purposes of further development of the analysis. We used the data collected in the first two weeks of enrolment to devise our own appropriate alarm limits for each patient. Data collected in the following three weeks was used to compare the number of alarms per day between the 'standard' limits used by CNWL and our personalised limits. False alarm was defined as any alarm triggered as a result of a physiological variable crossing pre-set limits and which led to initiation of a call by the tele-health nurse, but which was not considered to be an exacerbation by that nurse.

Statistical analysis

The analysis was performed in Microsoft Excel 2011 version 14.6.5 and SPSS 2013 version 22, and can be explained in four steps. First, limits were personalised for each patient by calculating the mean and standard deviation (SD) over the first two week period. Second, we tested alarm limits at mean ±1.5 SD and mean ±1.96 SD. Third, we compared the number of alarms initiated per day if the limits were set according usual standards (normal heart rate 60 – 100 beats min^{-1} (136) and normal saturations as $SpO_2\% \geq 95\%$) (137). compared to our 1.5 SD, and 1.96 SD limits. Fourth, we performed an Kruskal-Wallis test to assess if the difference between limits was significant ($P < 0.05$).

4.1.3 Results

Twenty-three patients were enrolled in this project, but the analysis was performed on only 10 patients as the remaining 13 were not stable during the first two weeks (and so it was not possible to calculate a baseline), or were not taking the measurements according to the protocol. The mean (SD) age of the 10 COPD patients was 69.3 (8.9) years, 70% males, 30% females, and the FEV_1% mean was 40% (19.1). In this pilot analysis, more detailed clinical information on the participants was not available, these data being collected for service development (not research) as described above. Table 5 below shows the alarm frequency for each algorithm. Results are expressed as alarms/day. Setting alarms of heart rate by individual parameters at ± 1.5 SD and ± 1.96 SD versus the standard limits (60 – 100 beats min^{-1}) did not alter the frequency of alarms per day significantly, but significantly decreased the frequency of oxygen saturation alarms when compared to the standard (95-98%).

Table 5. Alarms per patient per day.

HR 60 – 100 beats min^{-1}	HR ±1.5 SD	HR ±1.96 SD	P= Kruskal Wallis	SpO_2% 95 – 98%	SpO_2% ± 1.5 SD	SpO_2% ± 1.96 SD	P= Kruskal Wallis
0.175	0.15	0.08	0.435	0.4	0.03	0.013	0.006

4.1.4 Discussion

This study investigated the ability to decrease the number of alarms raised in a COPD tele-health programme by specifying the alarm limits for heart rate and oxygen saturation for each individual. Our findings demonstrated the efficacy of personalised limits for each patient for oxygen saturation, but not for heart rate.

Alarms can be used to alert the healthcare provider to deliver the health care needed to the patient. However, false alarms triggered from a patient can lead to alarm fatigue and/or unnecessary action. Increasing or decreasing the sensitivity of alarms in a hospital setting is controversial (138), it is important for homecare and tele-health services. False alarms in homecare/tele-health services can lead to an increase in unnecessary calls, decrease quality of care provided, and lose the patient's trust in the care provided. Therefore, customising the limits for each patient could be important.

There is no standardised or validated method for customising alarm limits for each individual. We have developed our approach carefully. The volume of calls/alarms per day due to oxygen saturation, but not heart rate, exceeding the pre-set limits decreased. The change in heart rate alarms per day was not statistically significant. The change in oxygen saturation alarms per day was statistically significant compared to the standards of limits set at ± 1.5 SD, and ± 1.96 SD. This could be explained through the standardised limits for heart rate (60 – 100 beats min^{-1}) being already wide, which makes

the number of alarms generated due to heart rate changes smaller than those generated because of oxygen saturation (range 95-98%). Hence, we did not show any statistically significant difference in the number of calls/alarms for the heart rate compared with the personalised method applied in this analysis.

In our study, there are two limitations. First, data were only available for a small sample, due to our focused interest on COPD patients only (the CNWL programme enrolled those with heart failure too). Second, the duration of monitoring after specifying the limits was not sufficient to test the sensitivity and accuracy of our method to pick up an exacerbation. Thus, we cannot comment if our ability to reduce alarms from oxygen saturation changes could result in missing exacerbations.

4.1.5 Conclusion

In this analysis, we have shown that alarm rates vary between arbitrary versus patient-specific thresholding. We were able to decrease false alarms and which would therefore reduce the volume of calls on the team by using patient-specific thresholding for oxygen saturation. Such an approach would require prospective testing to ensure exacerbations were not missed.

Because there was no further data available in this service, I sought alternative sources of clinical data and the next chapter describes an analysis using clinical data collected via modems from COPD patients treated with NIV.

4.2 Home Non-Invasive ventilation data

4.2.1 Aim

To assess the value of using data obtained from home NIV devices in clinical practice to predict exacerbations of COPD that result in hospitalisation.

4.2.2 Method

Design

An observational, quantitative, prospective analysis.

Target population

COPD patients on home non-invasive ventilation with an Internet modem.

Setting

Patients with COPD receiving NIV care at the Royal Free Hospital in London.

Statistical Consideration

Primary outcome

The primary outcome is whether patients' parameters on home NIV are statistically different to baseline prior to an exacerbation of COPD resulting in hospital admission

Participants

Data of eligible patients were accessed in the clinical environment by a member of the healthcare team. Participants consented to share their clinical data for research purposes.

Study Procedure

Patients receiving NIV at the Royal Free Hospital in London use NIV machines that include a memory card to record key data. The Royal Free database of home NIV parameters was examined, and any patient diagnosed with COPD on home NIV was highlighted. Clinical data were reviewed to ensure that the hospitalisation was due to a COPD exacerbation. We examined up to 12 months data prior to the day of hospital admission. All data from highlighted patients were exported to Microsoft Excel. Data collected at baseline included: age, sex, FEV_1, weight and height. Ventilator parameter data collected were: ventilator setting prescription (e.g. ventilator settings, mask type), respiratory rate (RR), tidal volume (Vt), minute ventilation (Ve), respiratory cycles triggered (%), and NIV usage (hours per day). Ventilator data were analysed over a six weeks period: a) two weeks stable phase (baseline: the two weeks preceding the two weeks of the pre-phase period), b) two weeks pre- hospitalisation phase, c) two weeks post-hospitalisation phase. Data were reviewed to investigate if and how ventilator parameters changed prior to an exacerbation resulting in a hospital admission as described below.

Statistical Analysis

The analysis used in this study was completed in Microsoft Excel 2011 version 14.6.5 and Statistical Package for Social Science Software ((SPSS) version 24, International Business Machines Index (IBM), USA) (SPSS). The baseline for each patient for each variable was set by calculating the mean

and standard deviation for the two weeks while the patient was stable (average for each day for 14 days). The time period 14 days prior to and after presentation to hospital with admission was then examined. Each variable for each patient was expressed as SD units away from that patient's baseline mean (Z score). The mean of these Z scores for each variable in the 18 patients was then plotted on a graph to examine the trend of each variable over time. Any variable outside the 95% confidence interval of the baseline mean ± 1.96SD was considered to be statistically significant at $p<0.05$. An ANOVA test was performed to examine the difference in mean between the three different phases: stable (14 days) represented on the Figures as a single day labelled as day -15, pre-exacerbation phase from day -14 to day -1, and the post-exacerbation phase from day 0 to day 14 (day zero is defined as the day of hospitalisation).

4.2.3 Results

4.2.3.1 Patients' characteristics

Fifty-seven COPD patients on home non-invasive ventilation were being monitored at the Royal Free. 29 were admitted to hospital because of a COPD exacerbation. Only 18 patients could be included in the analysis as the remaining patients (n=11) were not using the ventilator regularly (not enough data, e.g using the NIV for only a few hours per week). The mean (SD) age of the 18 included patients was 66.8 (±8.7) years, 61% were males, FEV_1% 41.9% (±14.7), and 61% were ex-smokers. Table 6 below shows the five NIV variables assessed on each patient in order to predict

hospitalisation due to COPD exacerbation, with the mean (SD) value across the population.

Table 6. Mean and SD of the variables monitored on non-invasive ventilation for every patient included at baseline.

Variable	Definition	Mean (SD) at baseline
RR	Respiratory rate breaths min^{-1}	16.4 (±0.3)
Vt	Tidal volume mL	609.4 (±18.0)
Ve	Minute ventilation L min-1	9.9 (±0.2)
Trigg%	Respiratory cycles triggered (%)	64.8 (±3.3)
Usage	NIV use (hours per day)	8.5 (±0.7)

4.2.3.2 Respiratory rate

Figure 7 below shows the variation of respiratory rate over the 28 days (two weeks before the hospitalisation due to COPD exacerbation and two weeks after, day -15 represents the baseline). Variability around the stable mean was considered to be within normal variation unless it crossed ±1.96SD away from the stable mean, which is zero SD. Despite respiratory rate variability increasing during the pre-and-post hospitalisation phases, variation was within 1.96SD. The mean of each phase was compared, which showed a statistically but not clinically significant difference in mean between the three phases (stable= 16.4 breath min^{-1}, pre= 15.9 breath min^{-1}, post= 15.8 breath min^{-1}), ($p<0.001$).

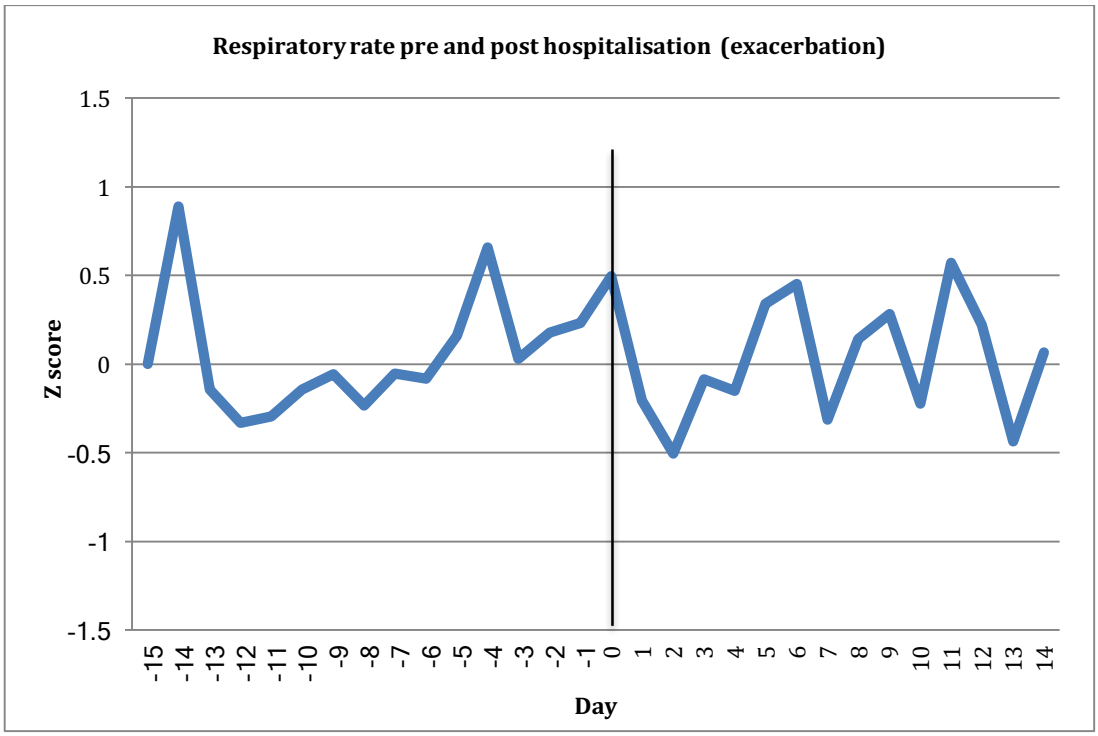

Figure 7. The mean of respiratory rate in 18 COPD patients. The Y–axis represent the 95%CI of the baseline mean value. whilst X–axis represent the monitored period (29 days). Day 0 represent the day of hospitalisation due to COPD exacerbation.

4.2.3.3 Tidal volume

Figure 8 below shows the tidal volume of the 18 COPD patients before and after hospitalisation due to COPD exacerbation. Tidal volume appeared to increase prior to exacerbation, reaching up to +1.35SD change from the baseline at day -2. However, this change was within 1.96SD; therefore, it is not a statistically significant increase. However, the mean difference across the three phases was statistically significant ($p<0.001$) between the pre-phase 653.0mL versus the stable-phase 609.4mL ($p<0.001$), and pre-phase versus the post-phase 622.7mL ($p=0.001$).

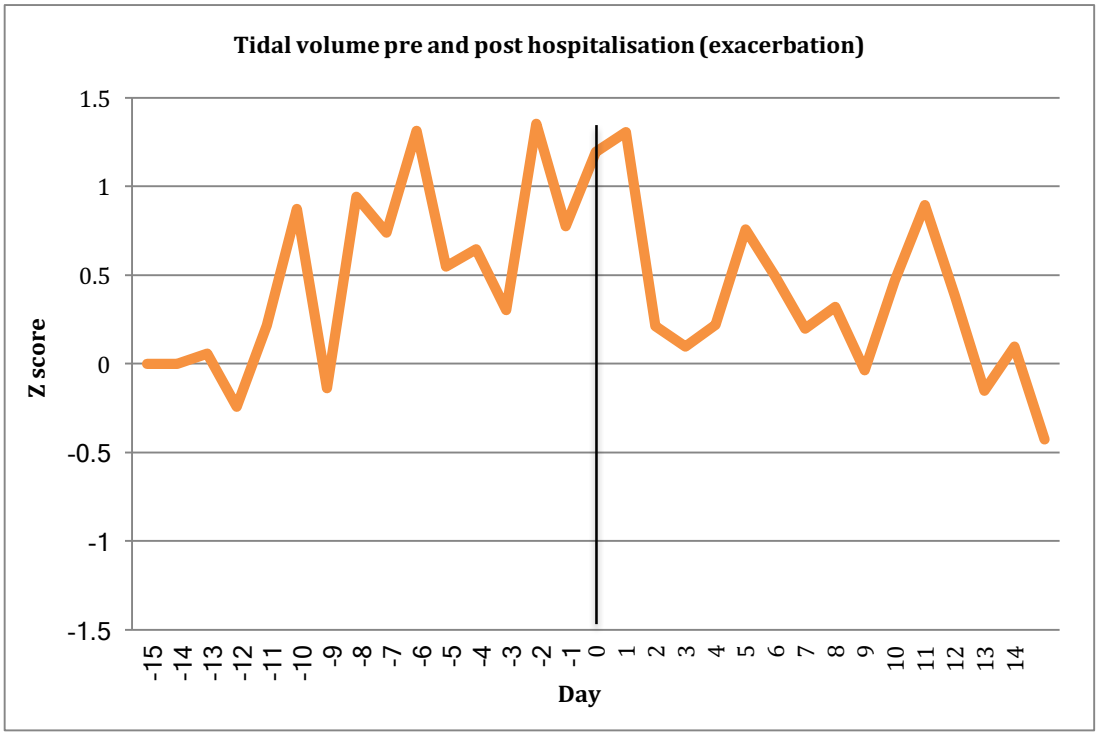

Figure 8. The mean of tidal volume in 18 COPD patients. Y–axis represents the 95%CI of the baseline mean value, whilst X–axis represent the monitored period (29 days). Day 0 represent the day of hospitalisation due to COPD exacerbation.

4.2.3.4 Minute ventilation

Figure 9 shows that minute ventilation did not cross the threshold of ±1.96SD away from the mean. Minute ventilation appeared consistently increased from day -8 before returning to baseline at day one. ANOVA testing showed a significant difference between the three phases ($p<0.001$). The difference was seen between the pre-phase 10.8 L min^{-1} versus the stable-phase 9.9 L min^{-1} ($p<0.001$), and between the pre-phase 10.8 L min^{-1} versus the post-phase 10.1 L min^{-1} ($p<0.001$).

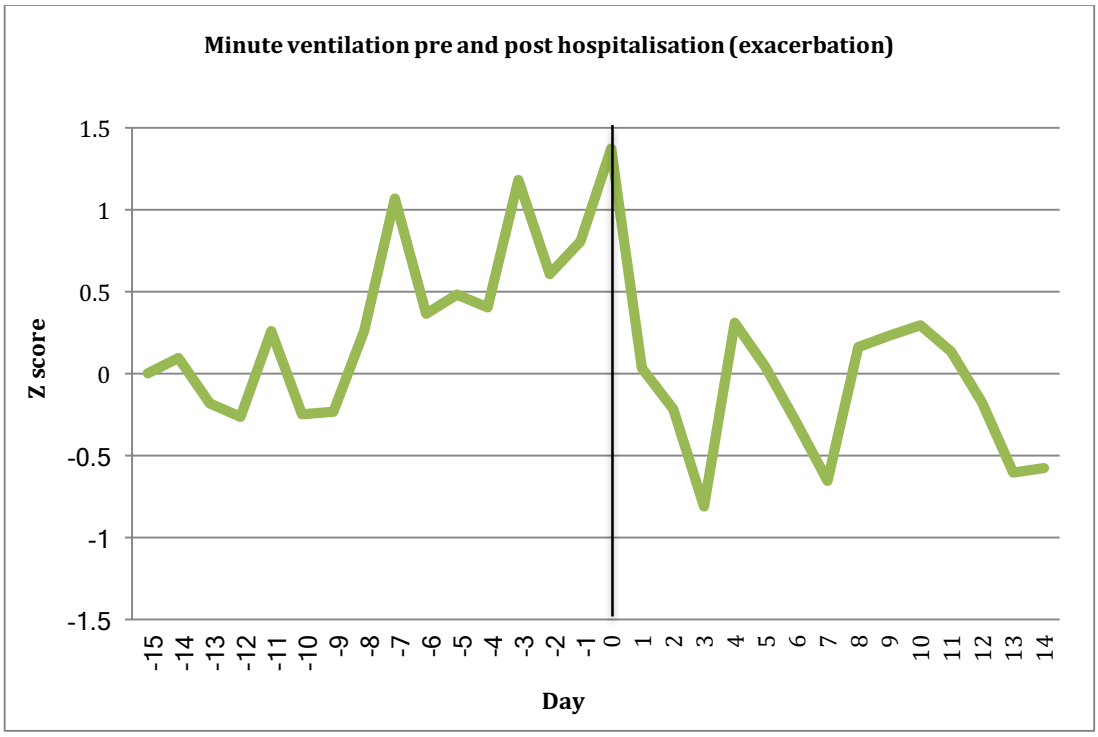

Figure 9. The mean of minute ventilation in 18 COPD patients. Y–axis represents the 95%CI of the baseline mean value, whilst X–axis represent the monitored period (29 days). Day 0 represent the day of hospitalisation due to COPD exacerbation.

4.2.3.5 Respiratory cycles triggered (%)

Figure 10 shows the percentage of respiratory cycles triggered over time pre-and-post hospitalisation due to COPD exacerbation. The trend of this variable was a gradual decrease from day -14 to day -11 before starting to increase until day zero. The observed change in day-to-day variation did not show any statistically significant change as this variation was within 1.96SD. However, the difference in mean between the three phases (stable-phase= 64.8%, pre-phase= 61.1%, post-phase= 63.6%) was statistically significant (p=0.004).

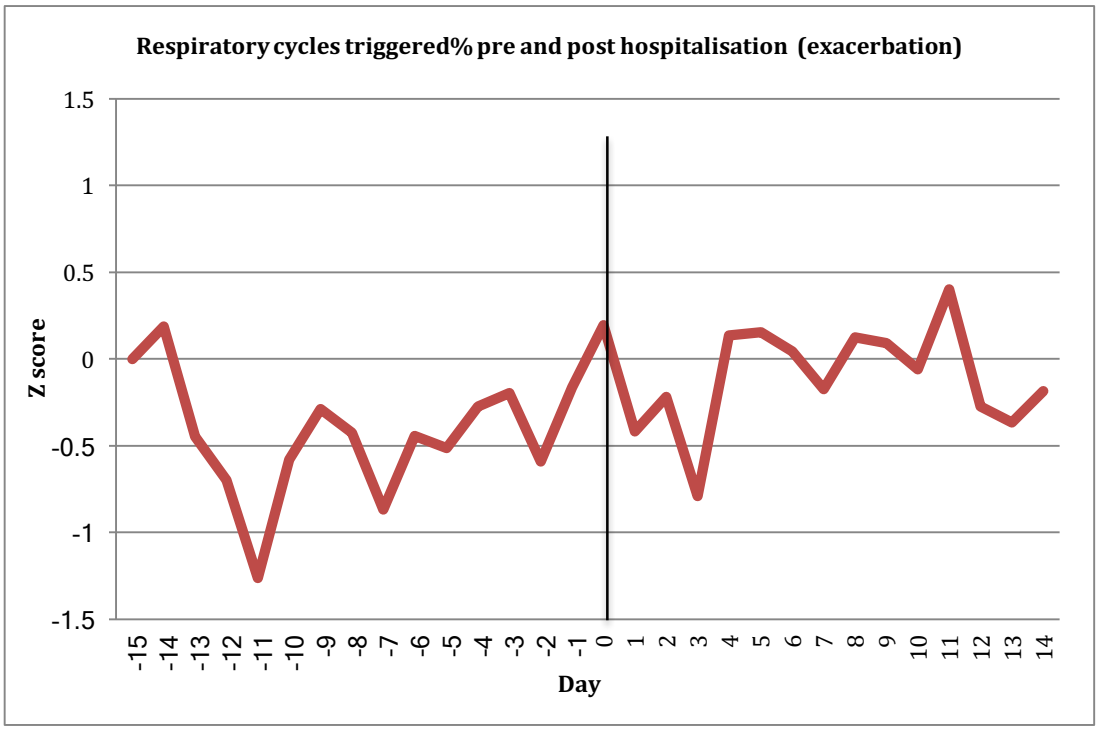

Figure 10. The respiratory cycles triggered % in 18 COPD patients. Y–axis represents the 95%CI of the baseline mean value, whilst X–axis represent the monitored period (29 days). Day 0 represent the day of hospitalisation due to COPD exacerbation.

4.2.3.6 NIV use (hours per day)

Figure 11 below shows that day-to-day variation in usage of NIV per day did not change significantly (within 1.96SD). However, the variability increased from day -7, and back to normal in day nine. Moreover, an ANOVA test showed no significant difference between the three phases: stable-phase= 8.5 hours/day, pre-phase= 9.1 hours/day, and post-phase= 9.0 hours/day.

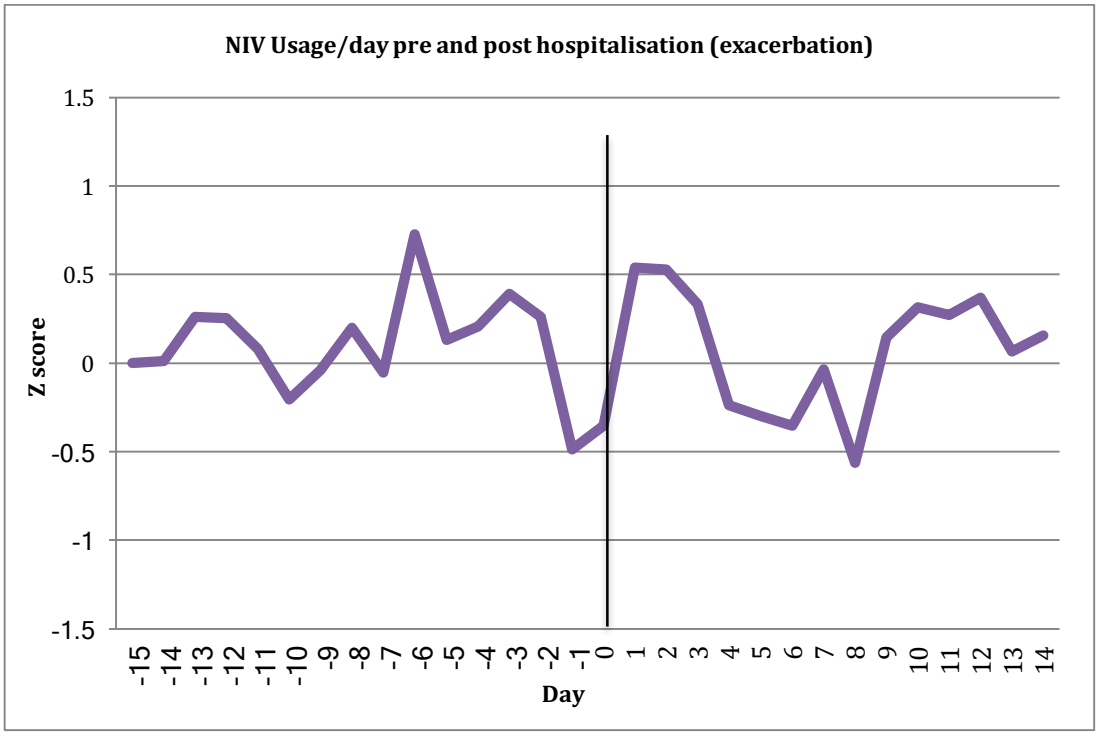

Figure 11. The non-invasive usage (hours/day) in 18 COPD patients. Y–axis represents the 95%CI of the baseline mean value, whilst X–axis represent the monitored period (29 days). Day 0 represent the day of hospitalisation due to COPD exacerbation.

4.2.4 Discussion

This study investigated the hypothesis that data extracted from remotely-monitored home NIV machines can predict a COPD exacerbation resulting in hospital admission. The method used to set the threshold (>1.96SD away from the stable mean) did not identify statistical changes in day-to-day variation prior to hospitalisation. None of the variables showed any statistically significant difference, despite suggestions of consistent changes in direction in some of the variables. However, the mean difference between the absolute measurements across the three different phases (stable-phase, pre-phase, post-phase) was statistically significant in all variables except NIV usage/day. Of the variables we assessed, tidal volume and minute ventilation have the best potential to provide assistance in earlier detection of events leading to hospitalisation in exacerbations of COPD in patients on NIV, as those variables were consistently increasing for consecutive days from day -8. However, variation in these alone did not cross the variation expected in 95% of stable days. Future work might explore different methods of detection using these variables, for example looking at statistical process control (SPC) chart methodology.

The usefulness of downloadable data from home non-invasive ventilators in COPD management is not well studied yet. Mansell et al. have reported that downloadable data from home NIV machines feeding into patient assessment has increased patients' compliance and usage of NIV (139). In this study, we examined the usefulness of using data from home non-invasive ventilators in detecting COPD exacerbations resulting in

hospitalisation. Our findings showed that the variability of each variable during the pre-phase was different than the stable phase at some point. The analysis showed that the mean difference of four variables during the pre-phase was statistically significant compared with the stable-phase, which suggests that deterioration could be identified through home NIV data monitoring. The change in respiratory rate and % triggered breaths trend was anticipated from the pathophysiology of exacerbation, as we would expect that increased respiratory rate would mean triggering more breaths. Although we could not show any significant change in the day-to-day variation, the trends in our data are similar to the Borel study, which noted a significant increase in three variables before exacerbation on patients receiving home NIV: RR, %triggered, and symptoms (116). This could be explained by differences in the way that thresholds were set between studies. Boral was based on the quartile method: any measurement below 25 or above 75 quartiles for two consecutive days was considered to be abnormal. This illustrates the importance of understanding the method used to identify unexpected variation from normal variation. Another study conducted by Yanez et al. showed that the mean respiratory rate of 30 COPD patients on home oxygen (not on NIV) progressively increased five days before hospitalisation due to exacerbation. Our findings are consistent with a recent study conducted by Blouet et al. in France. They reported that the %triggered breath tended to decrease before the day of admission due to COPD exacerbation (140). The decrease in %trigg could be due to some patients becoming fatigued/weak such that they are unable to trigger the

ventilator such that they fall back on to the pre-set backup ventilator settings. The tidal volume in Figure 13 was highest in the lead up to the exacerbation, and was lower for the 14 days post hospitalisation. Furthermore, as minute ventilation is dependent upon respiratory rate and tidal volume the findings are as we would expect. In our absolute (not Z score) data, the variability of the usage of NIV hours/day increased one week before hospitalisation and then returned back to baseline. This could be due to patients starting to feel unwell, which might lead to increase in use of their NIV. Further, NIV usage increased sharply on the day of hospitalisation, which suggests that patients were seen by a healthcare provider and were advised to use the ventilator. Borel et al showed that the usage of NIV was increasing before exacerbation, but could not show significant differences between pre-exacerbation and the stable-phase. However, Blouet et al showed that the variability of the daily usage of NIV was increasing before the day of hospitalisation.

Findings from this analysis showed that variables monitored via home NIV might be useful in identifying exacerbations that lead to hospitalisation. The ability to identify exacerbation earlier via home monitoring might decrease the burden of COPD on both patients and healthcare systems, as this would increase the potential for prompt access to healthcare and thus better outcomes. A study conducted by Wilkinson et al in 2004 showed that recovery of COPD patients from an exacerbation was associated with early access to treatment (although these patients had milder COPD and were not on NIV) (80). Rapid access and regular home monitoring could be achieved

by tele-monitoring, the effectiveness of which remains uncertain. At present, there is limited evidence to support monitoring of physiological variable to detect the deterioration of COPD patients before exacerbation in patients on home NIV. In our systematic review of physiological monitoring to predict COPD exacerbations, presented as Chapter 3, (118), only one study had evaluated the use of NIV parameters to detect exacerbation.

Strength and Limitation

We were not able to show that variables monitored on home NIV could be reliably used to identify changes prior to hospitalisation. However, our findings provide a support for further analysis to assess whether monitoring physiological variables could be used to facilitate earlier detection of events leading to hospitalisation due to COPD exacerbation. Well-constructed clinical trials are needed to evaluate the effectiveness of the method used.

4.2.5 Conclusion

We have shown that variables monitored by home ventilators have the potential to identify deterioration of COPD patients before hospitalisation, but that an approach analysing change using 95%CI of the mean was not sufficiently sensitive.

These data have been submitted for the upcoming American Thoracic Society conference in 2019.

These two chapter have used data collected in routine NHS practice. The availability of such data led us to question how widespread use of tele-health was in COPD, and thus we devised UK national and international surveys to assess this further, the subject of the next Chapter.

5 Utility and Methods of Tele-Health for COPD patients: UK National and International surveys

5.1 Use, Utility and Methods of Tele-Health for COPD patients in England and Wales: national survey

Easy access to two datasets, neither of which was using evidence based guidance to implement tele-health (because no such guidance exists, as found in the systematic review, Chapter 3) gave the perception that there may be widespread use of tele-health in COPD without an evidence base. I therefore set out to assess the extent of national (England and Wales), and international use of tele-health in COPD, exploring usage, technology employed, and methods to set alarms. The UK data has been accepted for publication in BMJ Open Respiratory Research journal, and the International data are currently in peer-review.

5.1.1 Aim

To summarise and explore the techniques that have been used by healthcare providers to implement tele-health in COPD in England and Wales and specifically on how to personalise the alarm limits for each individual.

5.1.2 Methods

A cross sectional survey consisting of 14 questions (see Appendix 2) was sent to 230 pulmonary rehabilitation (PR) organisations in England and Wales. The organisations were those taking part in the Pulmonary Rehabilitation arm of the National COPD Audit Programme, in September 2017. The organisations providing PR are most often community health providers, and therefore those most likely to be using tele-health

programmes. The survey was administered via SurveyMonkey™ in 2017. The questions were developed by the authors and tested for validity with local practitioners before a link to the questions was electronically distributed by e-mail to the PR organisations. A cover statement explained the purpose of this survey. We additionally advertised availability of the survey by circulating the weblink electronically via e-mail, Twitter, and LinkedIn. Ethics approval was not required. This study was a voluntary survey of health-care professionals. No patients were involved.

Questions were designed to cover five different aspects of tele-health in COPD: purpose of use, equipment type, clinician perceptions, variables monitored, and personalisation of alarm limits. For variables monitored, participants were asked to select all the variables that were monitored in their programme. We asked about heart rate, oxygen saturation, respiratory rate, blood pressure, temperature, peak flow, hours of CPAP use, hours of NIV use, step count, physical activity, metabolic equivalent data, sleep quality, phlegm, cough, breathlessness, wheeze, use of rescue medication, and participants had the option to add any variables that were not listed in free text. For any variables being used, participants were then asked how the alarm limit for each variable was set using a dropdown list (arbitrary, international guidelines, national guidelines, personalised to the patient, don't know, or not applicable). Participants who indicated that the alarm limit was personalised were asked how this was done. Participants did not have to answer all the questions.

With regard to questions on clinician perception, responses were graded on a Likert scale between 1.0 (not at all) and 10.0 (very much so). The Statistical Package for the Social Sciences (SPSS) version 24 was used to analyse the collected responses. P≤0.05 was accepted as the level of significance.

5.1.3 Results

65 participants completed the survey from 52 different NHS organisations. 24.0 (46.0%) of the organisations had used tele-health for COPD, and currently, 16.0 (31.0%) still provided tele-health services to patients with COPD. Of the respondents, 36/65 (55%) were physiotherapists, 23% nurses, 12% miscellaneous, 8% doctors, and 2% physiologists.

5.1.3.1 Perception

52/65 respondents completed the question about the usefulness of tele-health, where zero represented ‘not at all’ and ten represented ‘very much so’. The median and interquartile range (IQR) score was 5.0 (3.0 – 7.0) out of ten on the Likert scale. In respondents who had used (n= 28, median (IQR) 6.0 (3.0 – 7.0)) versus had not used (n= 24, median (IQR) 5.0 (2.0 – 7.0)) tele-health, there was a difference in score of 1.0 which was not statistically significant (P= 0.38).

5.1.3.2 Purpose and equipment

Of those who still used tele-health, 88% used it for baseline monitoring, 82% for early detection of exacerbations, 41% for monitoring recovery from an exacerbation, and 12% to assist patient adherence to a management plan. Some respondents used it for more than one indication. The equipment used (hardware) was a dedicated monitoring station in 50%, a smartphone/tablet app in 46%, and a fixed telephone in 36% of cases.

The variables being monitored in more than 50% of services are illustrated in Figure 12. This was most commonly oxygen saturation, heart rate and breathlessness.

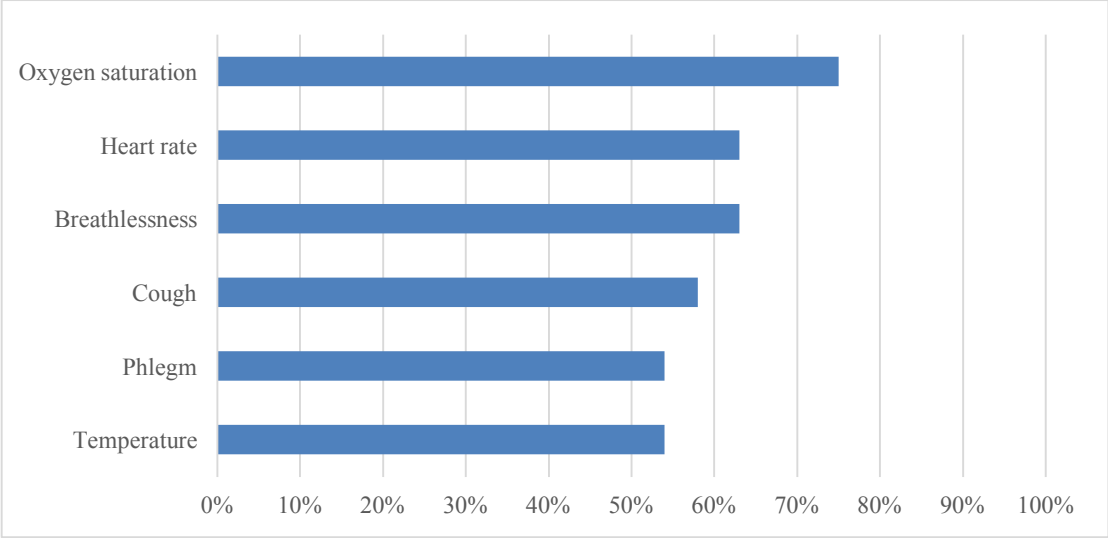

Figure 12. Variables monitored by tele-health providers.

5.1.3.3 Alarm limits

Table 7 shows how each respondent set the alarm limits for each variable they monitored. The majority selected either “National guidelines” (although no such guidance exists), or “personalised”. For personalisation techniques, the participants’ answers could be categorised in to one of four methods: observation taken at the time of set-up assessment, historical trends, calculation of a stable baseline, or a combination of set-up assessment and historical trend.

With regard to perceived sensitivity to detect exacerbation, 56% of 18 respondents thought their alarm technique was sensitive enough to identify exacerbation events. With regard to the efficiency of personalising alarm limits over arbitrary measures, the median (IQR) score on the Likert scale was 5.0 (4.0 – 8.0) in 17 participants, suggesting that there was no consensus on the utility of this approach.

Table 7. Participants' description of how alarm limits was set for each variable. Variables are ordered by frequency of use (see Figure 12).

Variables	Arbitrary/what feels right	Local guideline	National guideline	Personalised (based on data from that patient)	Not applicable	Total
Oxygen saturation	0% 0	13% 2	27% 4	53% 8	7% 1	15
Heart rate	0% 1	17% 2	8% 1	67% 8	8% 1	12
Breathlessness	8% 1	17% 2	17% 2	42% 5	17% 2	12
Cough symptoms	8% 1	8% 1	17% 2	42% 5	25% 3	12
Phlegm symptoms	9% 1	18% 2	27% 3	18% 2	27% 3	11
Temperature	0% 0	27% 3	46% 5	18% 2	9% 1	11
Blood pressure	0% 0	18% 2	18% 2	55% 6	9% 1	11
Wheeze	13% 1	13% 1	25% 2	25% 2	25% 2	8
Physical activity	14% 1	0% 0	0% 0	43% 3	43% 3	7
Use of medication	0% 0	14% 1	29% 2	29% 2	29% 2	7
Hours of NIV use	0% 0	20% 1	0% 0	20% 1	60% 3	5
Sleep quality	0% 0	0% 0	0% 0	75% 3	25% 1	4
Step count	25% 1	0% 0	0% 0	25% 1	50% 2	4
Peak flow	0% 0	0% 0	0% 0	33% 1	67% 2	3

Finally, we asked about the perceived proportion of 'false alarms'. These data are illustrated in Figure 13. The majority of participants thought that at least 40.0% of alarms were false.

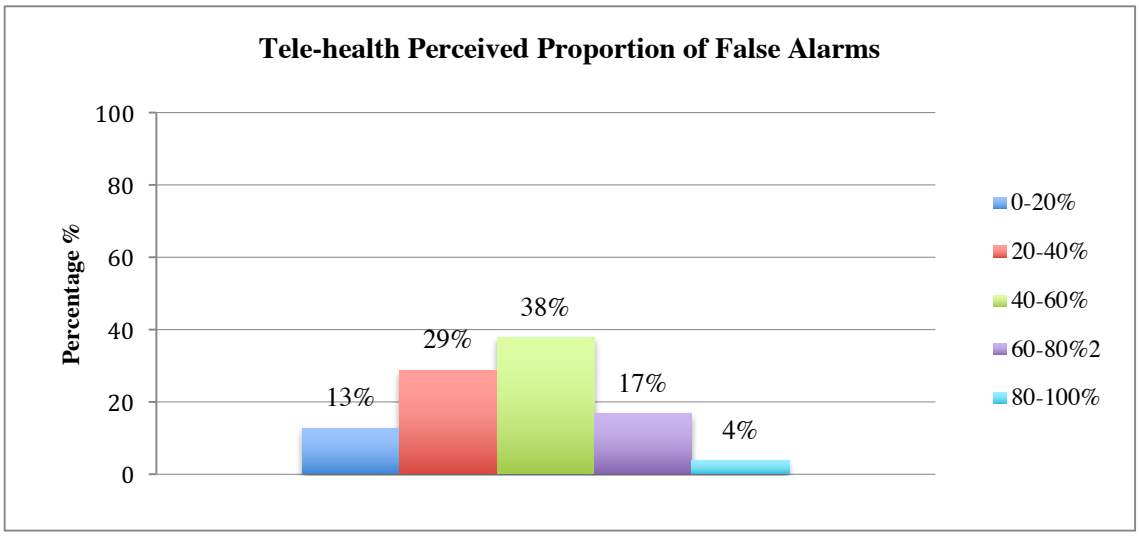

Figure 13. Perception of false alarms triggered from tele-health system.

5.1.4 Discussion

We have conducted a national survey to explore the use of tele-heath in COPD across England and Wales, and to summarise the techniques used by healthcare providers to personalise alarm limits for COPD patients enrolled in tele-health programmes. Our key findings are: of the 52 organisations that responded, 16 (31.0%) currently use tele-health, 28/52 (54%) of practitioners thought tele-health was useful in COPD (despite a high proportion of false alarms, and this did not vary by experience of use), tele-health is most commonly delivered from a fixed monitoring station, and the most common variables monitored are the oxygen saturation, heart rate, and breathlessness scores. Alarm limits for these variables were most commonly said to be personalised, using a variety of non-standardised

techniques, or guided by guidelines which, to the best of our knowledge, do not exist.

It is not clear how widespread the use of tele-health for COPD is in NHS clinical practice. Whilst around one third of organisations currently use tele-health, there is not a single record of all the organisations providing community COPD care, and therefore we cannot comment on the overall prevalence of use.

The usefulness of tele-health in COPD remains controversial. Based on this survey, most participants thought that tele-health was useful for managing COPD patients, despite an absence of robust clinical trial evidence and despite responses in this survey suggesting a high-proportion of false alarms. This suggests that further qualitative work is required to understand why some clinicians' perceptions do not match the available evidence. Some studies have shown positive results when tele-health is used in patients with COPD, for example reductions in emergency department visits, the need for non-invasive ventilation (NIV), hospital admissions, and hospital length of stay (111), which would indirectly affect the cost of COPD patients on healthcare. Other studies have not been positive. Ringbaek noted no significant benefit from tele-health for hospital admissions due to exacerbation or emergency department visits (141), and the randomised trial by Pinnock did not improve admission rates or quality of life (15).

The majority of participants who used tele-health in COPD used it for baseline monitoring and early detection of exacerbation. The variables

monitored by providers included symptoms and physiological parameters. Heart rate, oxygen saturation, and breathlessness were the most common variables monitored, each in >50% of services. In a pilot study in 2010, my Department demonstrated that daily physiological monitoring has the potential to provide early detection of COPD exacerbations (115). Other more recent studies have also shown the possibility of predicting COPD exacerbation via close monitoring of patients' symptoms and physiological variables (110, 131, 132). However, in my systematic review (Chapter 3) we concluded that there is currently insufficient information on how physiological parameters vary prior to exacerbation to support routine domiciliary monitoring solely for the prediction of exacerbations (118). Moreover, the draft revision of the National Institute for Health and Care Excellence (NICE) 2018 guideline for COPD has recommended not offering routine tele-health (physiological monitoring) for stable COPD patients, as evidence remains controversial (142). Regarding symptoms, in 2000, Seemungal noted a significant increase in respiratory symptoms (dyspnoea, cough, and sore throat) prior to exacerbation, with up to 64% of participants reporting increased dyspnoea on the day of onset of an exacerbation (122). Thus, monitoring breathlessness in a tele-health program might be valuable, but again there remains insufficient evidence to be able to recommend this routinely.

One major challenge of the use of tele-health is the question of how best to set alarm limits; too sensitive and there will be an excess of false alarms, not sensitive enough and exacerbations will be missed. The majority

of participants (59%) in this survey thought that > 40% of alarms received from tele-health systems were false, which is perhaps why some participants did not agree that personalising alarm limits made tele-health services more efficient, as a high number of false alarms could lead to alarm fatigue. This is consistent with published evidence which has shown that more than 72% of alarms are not clinically related (143). Triggered alarms could be due to many factors, which include technical issues, sensor mal-positioning, and changes in therapy. Even though there is no robust evidence to either agree or disagree with some of the techniques of how alarm limits were personalised, techniques were similar to those reported in our systematic review (118). This survey emphasises the need for testing, optimising and establishing a protocol for the personalisation of alarm limits. Many participants reported using national guidance to personalise limits, even though no such guidance exists.

Strengths and Limitations

Our survey has some limitations. We cannot be sure we reached a representative sample of all organisations providing tele-health. Tele-health may also be delivered by primary care, secondary care or private organisations. The survey was distributed electronically and no reminder was sent to fill and submit the survey, which may have contributed to the low response rate. Findings from this study should interpreted with a caution, as some questions were answered from a smaller number of participants. Furthermore, the responders to this survey could be biased towards either a

positive or negative view of tele-health in COPD depending on their previous experience and we have no way to assess this. The strength of our survey is that, to our knowledge, there is no previous survey assessing the use and purpose of tele-health for COPD in the NHS, or the techniques of personalisation of alarm limits. Further studies could consider, in particular, how tele-health has changed practice, and how patients are selected for tele-health programmes.

5.1.5 Conclusion

Around one third of responding community COPD services are using tele-health, believing it to be somewhat effective without robust evidence, monitoring a variety of variables and using a variety of hardware and techniques to set alarm limits with resultant high false-alarm frequency. This potentially increases clinical workload and actions; therefore, further robust research is needed to evaluate the utility of tele-health, and specifically the efficacy of personalising alarm limits and the validity of this approach in clinical practice prior to wider implementation in the UK NHS and more widely.

5.2 Use, Utility and Methods of Tele-Health for COPD patients: international survey

5.2.1 Aim

To summarise and explore the techniques that have been used by healthcare providers to implement tele-health in COPD worldwide, and specifically how to personalise alarm limits for each individual.

5.2.2 Method

We constructed a survey consisting of 15 questions (see Appendix 3) and advertised this to healthcare professionals by circulating a weblink electronically to international contacts and asking them to share this widely, Twitter, WhatsApp, and LinkedIn. The survey was administered via SurveyMonkey^{TM} between July 2017 and September 2017. The questions were developed by the authors and tested for validity with local healthcare professionals. A cover statement explained the purpose of this survey. Ethics approval was not required, as the study was a voluntary survey of health-care professionals, with no patient involvement.

Questions were designed to cover five different aspects of tele-health in COPD: purpose of use, equipment type, clinician perceptions, variables monitored, and personalisation of alarm limits. Regarding the monitored variables, participants were asked to select all those used by their programme. We asked about heart rate, oxygen saturation, respiratory rate, blood pressure, temperature, peak flow, hours of CPAP use, hours of NIV use, step count, physical activity, metabolic equivalent data, sleep quality,

phlegm, cough, breathlessness, wheeze, use of rescue medication, and participants had the option to add any variables that were not listed as free text. For any variables being used, participants were then asked how the alarm limit for each variable was set from a dropdown list (arbitrary, international guidelines, national guidelines, personalised to the patient, don't know, or not applicable). Participants who indicated that the alarm limit was personalised were asked how this was done. Participants did not have to answer all the questions.

With regard to questions on clinician perception, responses were graded on a Likert scale between 1.0 (not at all) and 10.0 (very much so). The Statistical Package for the Social Sciences (SPSS) version 24 was used to analyse the collected responses. $p \leq 0.05$ was accepted as the level of significance.

5.2.3 Results

138 participants completed the survey from 29 different countries, across six continents. The geographical location of the respondents is shown in Figure 14. The majority were from Saudi Arabia 30/138 (22.0%), United States 29/138 (21.0%), and with the rest 35/138 (25.0%) from elsewhere. Of the respondents, 58/65 (42%) were respiratory therapists, 27% doctors, 15% miscellaneous, 14% physiotherapists, and 2% nurses. 82/138 (59%) of practitioners had used tele-health for COPD, and currently, 45 (33%) still provided tele-health services to patients diagnosed with COPD.

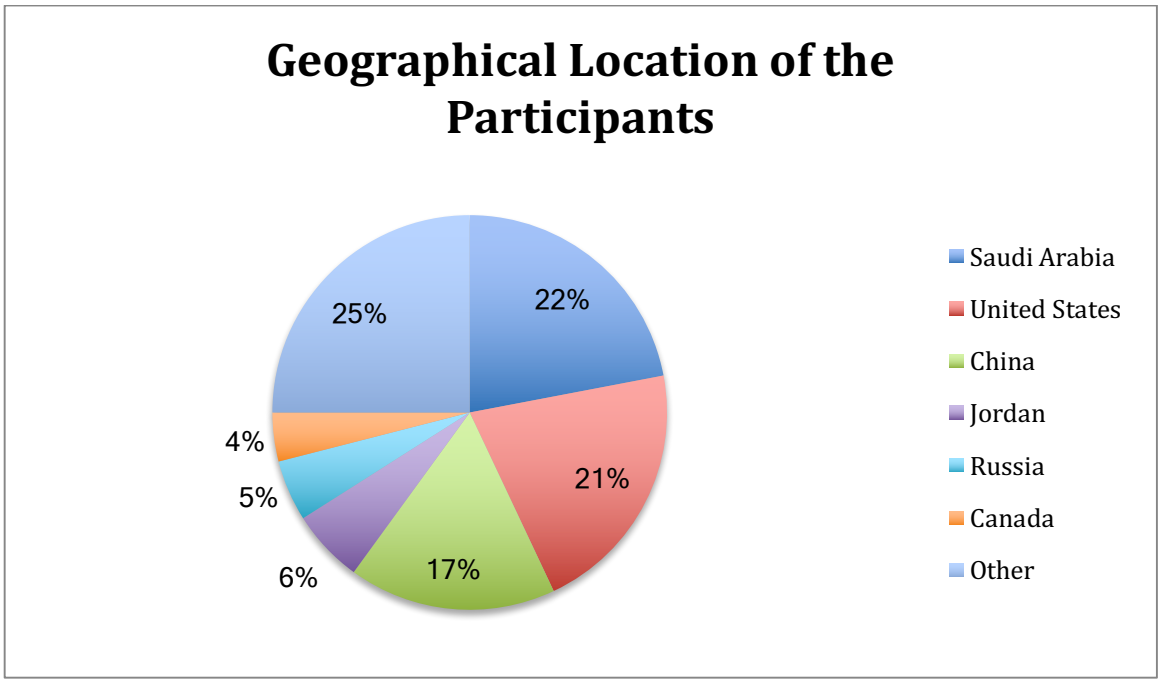

Figure 14. The geographical location of the respondents expressed in percentage.

5.2.3.1 Perception

In the opinion of the provider, 124/138 (90%) thought that tele-health was useful for COPD patients with a median (interquartile range (IQR)) score of eight out of ten (6.0 – 10.0) on the Likert scale. In respondents who had used (n= 81, median (IQR) 8.0 (6.0 – 9.0)) versus had not used (n= 43, median (IQR) 8.0 (6.0 – 10.0)) tele-health, there was no significant difference in perception of utility (P= 0.454). The providers' perspective of tele-health usefulness in COPD could be assessed from their written comments and was based on cost effectiveness, improved quality of life, self-management, motivation, early detection, prevention of exacerbation, monitoring of exacerbations, prevention of rehospitalisation, communication, assessment, and avoidance of hospital visits.

5.2.3.2 Purpose and equipment

Of the providers who still used tele-health, 43% used it for baseline monitoring, 34% for early detection of exacerbations, 31% for monitoring recovery from an exacerbation, and 18% for other purposes (some participants used it for more than one purpose). With regard to the equipment used (hardware), more than half of the participants (56%) used smartphones/tablet app, 28% fixed telephone, 16% monitoring station, 6% videophone and 5% miscellaneous.

Figure 15 shows the most frequent variables monitored among participants who used tele-health 73/82 (89.0%). Variables monitored varied between 1% (CAT & MRC score) to 86% (oxygen saturation), but only ten variables were reported as monitored by more than 50% of respondents. Six

were physiological variables and four were symptom variables. Oxygen saturation, heart rate and use of rescue medication were the most common variables.

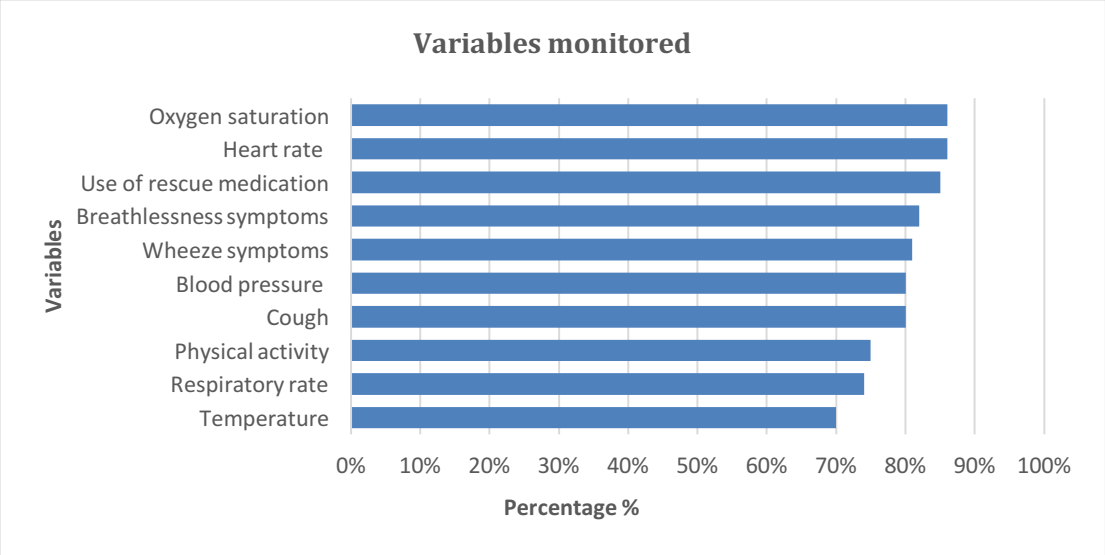

Figure 15. Variables being monitored by Tele-health providers.

5.2.3.3 Alarm limits

Table 8 shows how the alarm limits were set for each variable. Two techniques out of four were commonly selected by the participants: “National guidelines”, or “personalised”. With regard to the method of personalisation, the participants’ answers can be stratified into: observation taken at time of assessment, historical trend, age/gender, or set the upper/lower limits by 20% change on patient’s baseline.

Table 8. **The participant’s percentage of how alarm limit was set for each variable.**

Variables	Arbitrary/what feels right	Local guideline	National guideline	Personalised (based on data from that patient)	Don’t know	Not applicable	Total
Heart rate	6% 3	2% 1	53% 25	34% 16	4% 2	0% 0	47
Oxygen saturation	7% 3	2% 1	57% 26	28% 13	4% 2	2% 1	46
Use of medication	7% 3	5% 2	52% 23	32% 14	2% 1	2% 1	44
Respiratory rate	5% 2	5% 2	61% 26	21% 9	5% 2	5% 2	43
Breathlessness	12% 5	3% 1	49% 20	29% 12	2% 1	5% 2	41
Blood pressure	8% 3	10% 4	63% 25	15% 6	5% 2	0% 0	40
Cough symptoms	10% 4	8% 3	33% 13	43% 17	3% 1	5% 2	40

Wheeze	3% 1	3% 1	47% 18	40% 15	3% 1	5% 2	38
Physical activity	5% 2	5% 2	43% 16	32% 12	5% 2	8% 3	37
Hours of NIV use	6% 2	6% 2	39% 14	31% 11	6% 2	14% 5	36
Temperature	6% 2	8% 3	70% 25	11% 4	3% 1	3% 1	36
Phlegm symptoms	6% 2	6% 2	29% 10	44% 15	6% 2	9% 3	34
Peak flow	9% 3	3% 1	38% 13	27% 9	3% 1	21% 7	34
Hours of CPAP use	3% 1	9% 3	44% 14	22% 7	6% 2	16% 5	32
Step count	3% 3	6% 3	41% 3	25% 3	3% 3	21% 3	32
Sleep quality	3% 1	7% 2	36% 11	36% 11	7% 2	13% 4	31

With regard to sensitivity of technique to detect exacerbation, 92% of participants responded and 63% thought their alarm technique was sensitive enough to identify exacerbation events. 82/82 participants believed that personalised rather than arbitrary alarm limits made their service more efficient, with a median (IQR) score of seven out of ten (6.0 – 8.0) on the Likert scale.

Figure 16 shows the perceived proportion of false alarms generated from tele-health systems in 81/138 (59%) participants. The majority believed that 20 – 60 % of alarms were false.

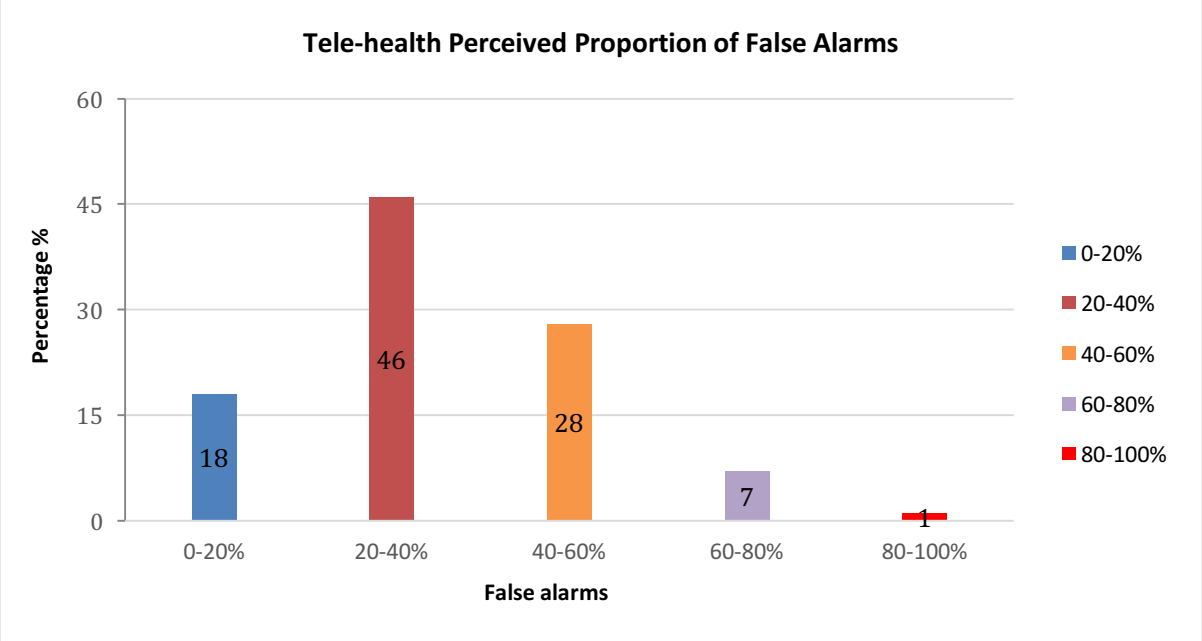

Figure 16. Perceived percentage of false alarms triggered from tele-health systems.

5.2.4 Discussion

We conducted an international survey to explore the use of tele-health in COPD, and to summarise the techniques used by healthcare providers to personalise alarm limits for COPD patients enrolled in tele-health programmes globally. Our key findings are: of the 138 responders, 45 (33%) currently use tele-health, 90% of practitioners thought tele-health was useful in COPD, tele-health is most commonly delivered from a smartphones/tablet app, and the most common variables monitored are oxygen saturation, heart rate and use of rescue medication. The majority set alarms limit for these variables based on national guidelines – though we know of no such guidance. For alarm limit personalisation, different methods were reported but with no evidence base, which at present does not exist, particularly for physiological variables.

Even though the efficacy of tele-health in COPD is still in question, the majority of providers believed that tele-health was beneficial for COPD patients, despite the lack of robust evidence, and despite a diverse range of methods and alarm techniques being used. These findings suggest the need for more studies to evaluate why providers' perceptions do not match the current evidence, and the need for greater awareness of providers about tele-health and how objectively to assess its outcomes. Ayatollahi et al. reported that the lack of knowledge found in healthcare providers can influence their perception of benefit (144).

The provision of tele-health service could be achieved through several applications. Based on our findings, smartphones/tablet hardware were the

most commonly used. The potential for better monitoring of COPD patients via smartphones is plausible. Ding et al. in 2014 reported that using a smartphone application contributed to a decrease in the number of hospital admissions and emergency department attendances as they could distinguish changes in symptoms prior to an exacerbation (145). A recent meta-analysis noted that patients monitored via smartphones tended to have fewer COPD exacerbations compared to conventional care (146). Further, Williams et al. demonstrated the positive impact of using smartphone apps in increasing the level of self-management and awareness of COPD patients (147).

Heart rate, oxygen saturation, and use of rescue medication were the most common variables being monitored. In the pilot study conducted by my Department in 2010, we were able to detect a significant change in heart rate and oxygen saturation before exacerbation onset (115). The maximum change in heart rate was an increase of 3.09SD and the maximum decrease in oxygen saturation was -1.24SD at day 2 of exacerbation. Moreover, in my systematic review (Chapter 3), we summarised the potential of monitoring physiological variables for detection of exacerbations (118), given the current definition of an exacerbation as an acute worsening in respiratory symptoms (1). This suggests there needs to be clear tele-health guidelines for COPD to determine which variables should be monitored, and the need for more clinical trials assessing the potential for physiological variables to provide early detection of a COPD exacerbation, and to distinguish this from day-to-day symptom variation.

Another key factor that may improve the efficacy of tele-health service is the setting of alarm limits. Our findings showed that the majority of providers (89%) thought personalising the alarm limits for each patient improved the care provided, and 63% thought their technique was sensitive to detect exacerbations, at the expense of a high proportion of false alarms. The latter could lead to alarm fatigue (148), which therefore may affect service quality, patient trust, and cost-effectiveness. Studies have shown that most of the time, alarm limits are breached not because of health-related issues, rather because of technical malfunctions, sensor malpositioning or changes in therapy (143). Clearly, well-constructed trials will be needed to establish standardised guidelines for personalising alarm limits for COPD patients enrolled in a tele-health service as the reported personalisation methods from the providers are not scientifically proven, even though they were similar to those previously reported in our systematic review.

Strengths and Limitations

Our survey has some limitations. The responsibility for delivering tele-health services for COPD worldwide is not clear; thus, we cannot be sure if the survey reached a representative sample of appropriate providers. The strength of our survey is that, to our knowledge, no previous survey investigating the techniques used for personalisation alarm limits, nor the purpose of the use of tele-health with COPD, have been conducted worldwide.

Differences between UK and International Practice

Comparing both surveys, findings showed that the percentage of practitioners who thought tele-health was useful in COPD internationally was higher than in England and Wales. Globally smartphone/tablet apps were the most used method, whereas in England and Wales a fixed monitoring station was the most reported method. With regard to variables monitored, internationally, heart rate, oxygen saturation, and the use of rescue medication were the most variables monitored; whilst in England and Wales, participants reported that heart rate, oxygen saturation, and breathlessness score were the most frequently monitored variables. Globally the alarm limits were most frequently set based on guidelines, from known normal limits (for example, HR 60 – 100 beats min^{-1}), whereas in England and Wales limits were most often set based on non-standardised techniques. However, both national and international participants reported that the majority of alarms received via tele-health were false.

The differences between national and international surveys are interesting, and not fully explained. We hypothesise that the differences could be due to various reasons. First, regulation of tele-health services and to what extent suggested tele-health services comply with data protection laws is likely to differ between countries. Second, different countries may have different licensure rules for medical equipment, which in some countries might not exist yet. This would affect choice of device, the method of implementation and the scope of tele-health services. Third, we would need to consider different reimbursement systems. This might be not an issue in some

countries such as the USA as some tele-health services are partially covered by health insurance. However, in the UK, tele-health is not well adopted yet (and explicitly not supported by the 2018 NICE Guidance), which is driven by the lack of evidence about cost-effectiveness and benefits. Finally, we need to consider the local health care system and how usual care is offered and delivered, which would impact the need of other health solutions.

5.2.5 Conclusion

Twenty-nine different countries use tele-health for managing COPD and therefore there is widespread international use of tele-health in COPD. The majority of providers thought tele-health was effective despite evidence to the contrary. Different types of hardware and different non-standardised techniques to personalise alarm limits are used.

6 Continuous Overnight Monitoring to Predict Exacerbations of COPD: a randomised controlled trial.

This chapter describes my main project: a randomised controlled trial to assess whether overnight versus once daily monitoring of physiological variables would provide better detection of COPD exacerbations. Part of the findings of this chapter have been submitted as abstract to the 2019 American Thoracic Society conference, and a full paper is in preparation.

6.1 Aim

To study the possibility of predicting a COPD exacerbation by monitoring patients' physiological parameters overnight, thus removing non-COPD related effects, for example, anxiety and exercise from the physiological signal. Furthermore, we aimed to compare this overnight measurement strategy to once-daily measurement of physiology.

6.2 Methods

Research design

The design of this study was observational, quantitative, longitudinal and prospective in the form of a randomised controlled trial.

Study setting

Participants were recruited from the Royal Free Hospital, Central and North West London NHS Foundation Trust, and Central London Community Healthcare NHS Trust. Participants in all centres were approached in COPD clinics, and pulmonary rehabilitation classes (PR)).

Method of sampling

A convenience sample was approached.

Eligibility criteria:

Inclusion criteria

- Patient diagnosed with COPD (smoking history of ≥10 pack years and $FEV_1/FVC < 0.7$ post-bronchodilator).
- Patient who had two or more self-reported moderate or severe COPD exacerbations in the past 12 months.
- Patient who can use study equipment and attend appointments.
- Can communicate in English.

Exclusion criteria

- Patients who were diagnosed with obstructive sleep apnoea (through a self-report and/or result of Epworth and Stop-Bang questionnaires; Appendices (Appendix 4 and Appendix 5) – because this would affect overnight oximetry.
- Patient with co-morbidity preventing taking part.
- Patients already involved in an on-going research study.

Statistical considerations

Primary outcome

The primary outcome was the difference in time to receive treatment from exacerbation onset as defined by symptoms (CAT questionnaire score), compared to exacerbation onset as defined by change in physiology.

Secondary outcomes

- Participants' compliance with continuous monitoring.
- How physiological parameters change during exacerbation recovery.

Power calculation

In previous work from my Department (115), changes in physiological parameters measured once per day were detectable two days before exacerbation onset, and there was an average delay of two days between symptoms first becoming abnormal and the patient receiving treatment. If overnight monitoring increased the sensitivity of monitoring such that we were able to detect the exacerbation three and a half days before exacerbation onset we would need 22 patients in each group to have 90% power at $p<0.05$. However, this assumes all patients will experience an exacerbation and, again, previous data by Hurst et al. showed that 84% of frequent exacerbators will have an exacerbation in one year (74). Therefore, if 16% will not exacerbate in one year, 32% won't exacerbate over a 6/12 study (assuming events are random). Therefore, we increased our recruitment to account for this, 44x 1.32= 58 patients in total. To allow for 10% drop-out we increased this further to 64 patients.

Study procedures

Recruitment of participants

Ethical approval obtained from the National Health Service (NHS) Health Research Authority. A member of the health-care team approached eligible patients in the clinical environment. Interested patients were provided with project literature and later contacted by the research team (Appendix 6). Patients who agreed to participate or who were interested in participating were given an invitation to attend a recruitment visit. All the patients participated in this study have given a written informed consent (Appendix 7).

Randomisation Methods

Sealed envelopes were used for the randomisation. Each envelope had a folded paper inside indicating control arm (once-daily measurement) or experimental arm (overnight measurement).

Recruitment visit

Each recruitment visit was divided into four parts. First, a full study description was delivered to the participant. Next, participants who agreed to participate in the study were asked to fill out the consent form and sign it. Third, we collected the study information: contact information and demographic data such as age, sex, weight, height, FEV_1, FVC, number of past exacerbations, history of smoking, co-morbidity, Medical Research Council (MRC), and medications taken, if any. We administered STOP-Bang

and Epworth questionnaires (further detail below) concerning obstructive sleep apnoea. Finally, participants were randomised (sealed envelope) and the researcher instructed the participant on how to use the finger pulse oximeter or wearable pulse oximeter device (based on randomisation selection), peak expiratory flow meter, diary card, and the COPD Assessment Test (CAT) questionnaire (to ensure that they understood the questions), as well as instruction on how the data should be collected. Further details of the trial methodology and these assessments appear in the sections below.

Epworth Sleepiness Score (ESS)

ESS is a simple questionnaire designed to assess sleepiness levels during daytime (149). It consists of eight different situations. Patient should rate each situation between 0 – 3 points. Points are then added up to give a total score. A score of 10 points or more was considered abnormal (Appendix 4).

STOP-Bang

STOP-Bang is a self-administered questionnaire that assists in screening for patients at risk of obstructive sleep apnoea (150). It consists of eight questions. Each question should be answered with a yes/no answer. Questions answered with yes were given one points, with zero for questions answered with no. Patient at highest risk of obstructive sleep apnoea have a high score: low risk 0 - 2, intermediate risk 3 - 4, high risk 5 - 8 (Appendix 5).

Medical Research Council (MRC)

MRC is a dyspnoea scale that is designed to evaluate the impact of breathlessness on daily activity (151). The scale consists of five grades (1 – 5). Patients were asked to choose the grade that describes them the best (Appendix 8).

COPD Assessment Test (CAT)

CAT is a questionnaire consisting of eight items designed to measure the impact of COPD on patients' health (152). Each item has six points (0 – 5 points) to indicate the severity. Points are then summed to be presented as one score. A higher score means worse COPD impact on patients' health (Appendix 9).

Overnight (experimental) group:

Each participant in this group was given a wristband pulse oximeter (Nonin 3150), CAT questionnaire, peak flow meter, and diary card. Each participant was instructed to wear the wrist pulse oximeter before sleeping, and to remove it as soon as they woke up in the morning (however, it should not be removed if they wake during the night to use the bathroom). Participants were asked to perform the peak expiratory flow and CAT questionnaire every morning at the same time and before taking any medications. The pulse oximeter data were stored in the device (internal memory), and then downloaded at scheduled visits.

Once-daily (control) group:

Each participant in the once-daily (control) group was given a finger pulse oximeter (Nonin G92), CAT questionnaire, peak expiratory flow meter device, and diary card to record the data (heart rate, oxygen saturation %, and peak expiratory flow) every day in the morning. Participants were instructed to take all the measurements at the same time every day, in the morning before taking morning medications, if any and after resting for ten minutes. For pulse-oximetry, participants were asked to record the measurements after wearing the finger probe for at least 30 seconds.

Once-daily (control) group and overnight (experimental) group:

The participants kept the CAT questionnaires, plus the diary card and we collected these during the in-person scheduled visits or if they had an exacerbation. Data recorded in the first week were not included in the analysis. During the first two weeks, data were closely monitored to ensure that the participants were using the equipment properly and reporting the date accurately. Participants were instructed to call us if they developed an exacerbation, or if they developed any medical problem resulting in hospitalisation or emergency visits. Monitoring was continued through the exacerbation until recovery at which point the equipment was returned and participation was then completed. Equipment was removed from any participant that did not develop an exacerbation within six months.

Statistical Analysis

Normally distributed data are reported as mean (SD) and non-parametric data as median (IQR). Groups were compared by t-test, Mann-Whitney U test and Chi-square as appropriate, and relationships between variables assessed using Pearson or Spearman Rank as appropriate. ANOVA test and Kruskal–Wallis test were used as appropriate to assess the difference between the three different phases (stable, pre-exacerbation, and post-exacerbation). Each variable for each patient was expressed as SD units away from that patient's baseline mean (Z score). The mean of these Z scores for each variable in the 27 patients was then plotted on a graph to examine the trend of each variable over time. Any variable outside the 95% confidence interval of the baseline mean ± 1.96SD was considered to be statistically significant at $p<0.05$. Analysis of the data was performed using the software Statistical Package for the Social Sciences (SPSS), Version 24.

Monitoring and Follow-up plan

- One week after the first day of the study, reminder instructions via phone.
- Participants were given a contact card if they have any questions or issues regarding the study or equipment.
- In-person visits were scheduled at two weeks, three months, and six months to evaluate the participant's data.

6.3 Results

6.3.1 Patients characteristics

One hundred eighty-six COPD patients were approached to take part in this study. 47% of the patients agreed and thus 88 COPD patients were recruited and randomised to either one measure per day (control) group, or the continuous overnight monitoring (experimental) group, both monitored for a maximum of six months or until they reported an exacerbation episode (whichever was sooner). Of those 88 patients, five patients from the experimental group were excluded from the study and the analyses (Figure 17) because they subsequently required oxygen therapy, and/or acquired a diagnosis of OSA.

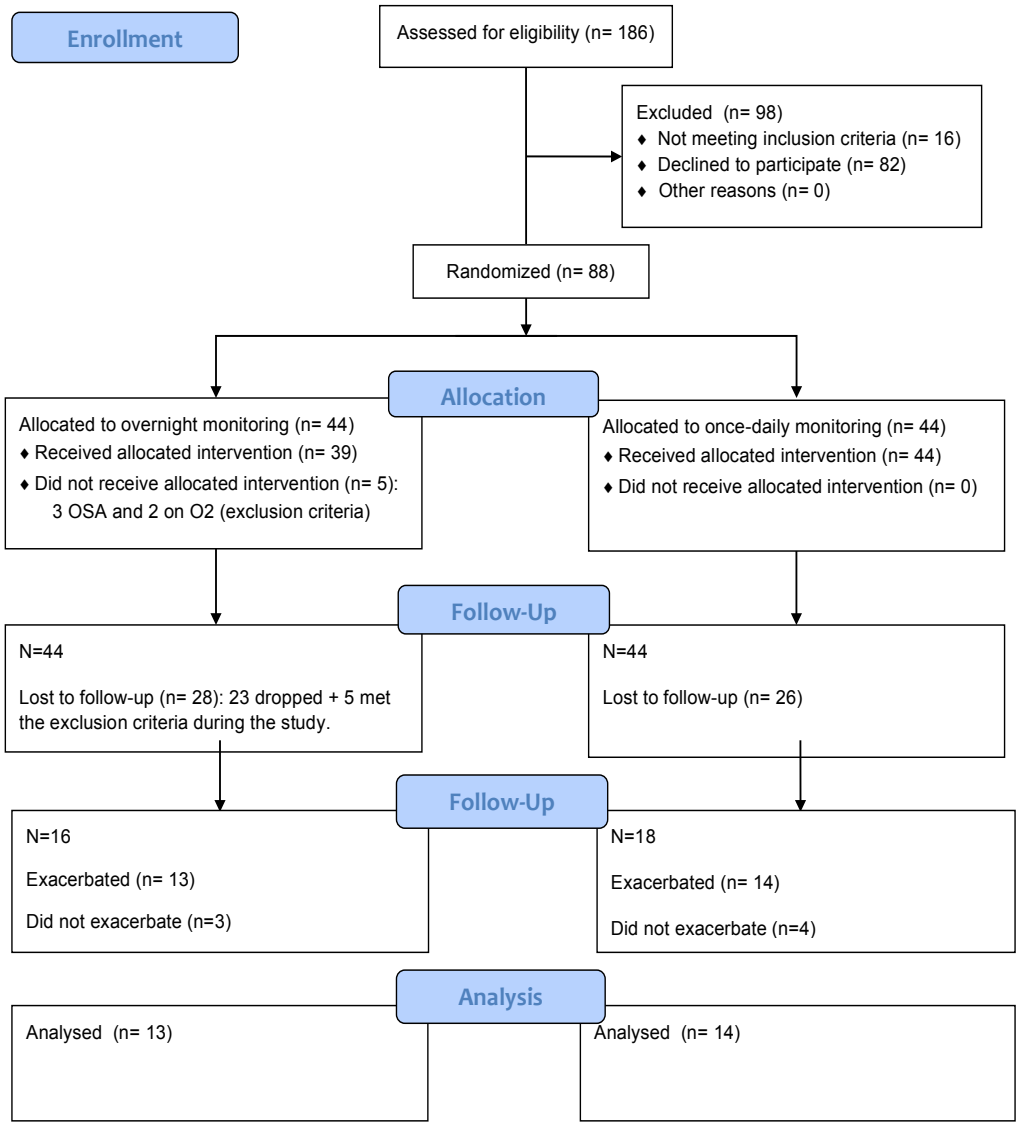

Figure 17. Consort flow diagram (OSA: obstructive sleep apnoea, O_2: oxygen).

The patients' baseline characteristics are presented in Table 9. The mean (SD) age of the patients was 70.6 (±8.1) years. 52% were female (n=43), the mean (SD) BMI was 26.7 (±5.9) kg/m^2, and the mean (SD) percentage FEV_1 was 53.0% (±18.5). The majority of the patients were ex-smokers (77%). 52% of the patients reported that they were living alone. The median (IQR) number of COPD exacerbations within the past 12 months was 2.0 (1.0 – 3.0). The median (IQR) number of hospitalisations due to COPD exacerbation within the past 12 months was 0.0 (0.0 – 0.0). The mean (SD) Charlson index comorbidity score was 4.1 (±1.2). The mean (SD) Medical Research Council breathlessness (MRC) score was 2.9 (±0.8). With regard to sleepiness score (Epworth), and risk of obstructive sleep apnoea score (STOP-Bang), the majority of patients were within normal range (92%) and intermediate risk (51%), respectively.

Table 9. Patients' demographics and clinical measures (n=83 COPD patients).

Demographics	
Age years	70.6 (±8.1)
Gender (Female, No. %)	43 (51.8)
BMI kg/m^2	26.7 (±5.9)
Smoking status No. (%)	
Ex-smoker	64 (77.1)
Current smoker	19 (22.9)
Do you live with someone No. (%)	43 (51.8)
Clinical measures	
FEV_1 L	1.2 (±0.4)
FEV_1%	52.9 (±18.6)
FVC L	2.6 (±0.8)
FVC %	83.7 (±21.7)
FEV_1/FVC %	51.9 (±11.7)
MRC	2.9 (±0.8)
Number of exacerbation /year	2 (1 – 3)
Number of hospitalisation /year	0 (0 – 0)
Charlson comorbidity index	4.1 (±1.2)
STOP-Bang No. (%)	
Low-risk	19 (22.9)
Intermediate risk	42 (50.6)
High risk	22 (26.5)
Epworth No. (%)	
Normal range	76.0 (91.6)
Borderline range	3.0 (3.6)
Abnormal range	4.0 (4.8)

Baseline data reported as mean (SD) or median (IQR) unless stated otherwise.

Table 10 below shows the characteristics of the patients who exacerbated (n= 27), divided in to the two randomised groups. No statistically significant differences were found between the once-daily (control) group and the overnight (experimental) group, suggesting the groups were similar at baseline.

Table 10. Patients' demographics and clinical measures (n=27 COPD patients).

Demographics			
	Once-daily arm (n=14)	Overnight arm (n=13)	P value
Age years	72.2 (±2.6)	70.7 (±2.9)	0.675
Gender (Female, No. %)	10.0 (71)	6.0 (46)	0.182
BMI kg/m^2	25.6 (±1.4)	25.5 (±1.9)	0.977
Smoking status No. (%)			0.918
Ex-smoker	11 (79.0)	10 (77.0)	
Current smoker	3 (21.0)	3 (23.0)	
Do you live with someone No. (%)	7 (50.0)	8 (62.0)	0.547
Clinical measures			
FEV_1 L	1.0 (±0.3)	1.1 (±0.5)	0.632
FEV_1%	53.5 (±17.7)	44.8 (±18.2)	0.515
FVC L	2.3 (±0.7)	2.5 (±0.9)	0.304
FVC %	82.9 (±17.7)	77.8 (±15.6)	0.521
FEV_1/FVC %	52.6 (±14.5)	50.8 (±10.7)	0.719
MRC	2.6 (±0.2)	2.9 (±0.2)	0.343

Number of exacerbation /year	1.5 (1 – 2)	2.0 (1 – 3)	0.430
Number of hospitalisation /year	0 (0 – 0)	0 (0 – 0)	0.374
Charlson comorbidity index	4.0 (±0.3)	4.5 (±0.2)	0.262
STOP-Bang No. (%)			0.353
Low-risk	5 (36.0)	3 (23.0)	
Intermediate risk	7 (50.0)	5 (38.0)	
High risk	2 (14.0)	5 (38.0)	
Epworth No. (%)			0.127
Normal range	14 (100)	11(85.0)	
Abnormal range	0 (0.0)	2 (15.0)	

Baseline data reported as mean (SD) or median (IQR) unless stated otherwise.

6.3.2 COPD Assessment Test (CAT)

First, we looked at changes in CAT score to understand the symptom changes during the exacerbations we had captured. The CAT score for all the patients (once-daily and overnight group together) was monitored pre-and-post exacerbation onset (defined by start of treatment). Figure 18 shows the CAT score from two weeks prior to exacerbation (day -1 to day -14) exacerbation onset (day 0: defined here as start of treatment) and two weeks after exacerbation onset as the patient recovers with treatment (day 0 to day 13). Day -15 on the graph represents the mean of the stable period, defined

as the mean of two weeks measures of CAT score while the patients were stable. The mean (SD) CAT score for the 27 COPD patients at baseline was 15.6 (±0.4) points. Using a 1.96SD change ($p<0.05$); therefore, any score >1.96SD units away from the mean (zero) was considered statistically significant above baseline. In Figure 18, the CAT score crossed the pre-set statistical threshold from day -5 to day 13. The increase of CAT score was highest on day zero (the day of exacerbation) with a change of +6.2SD.

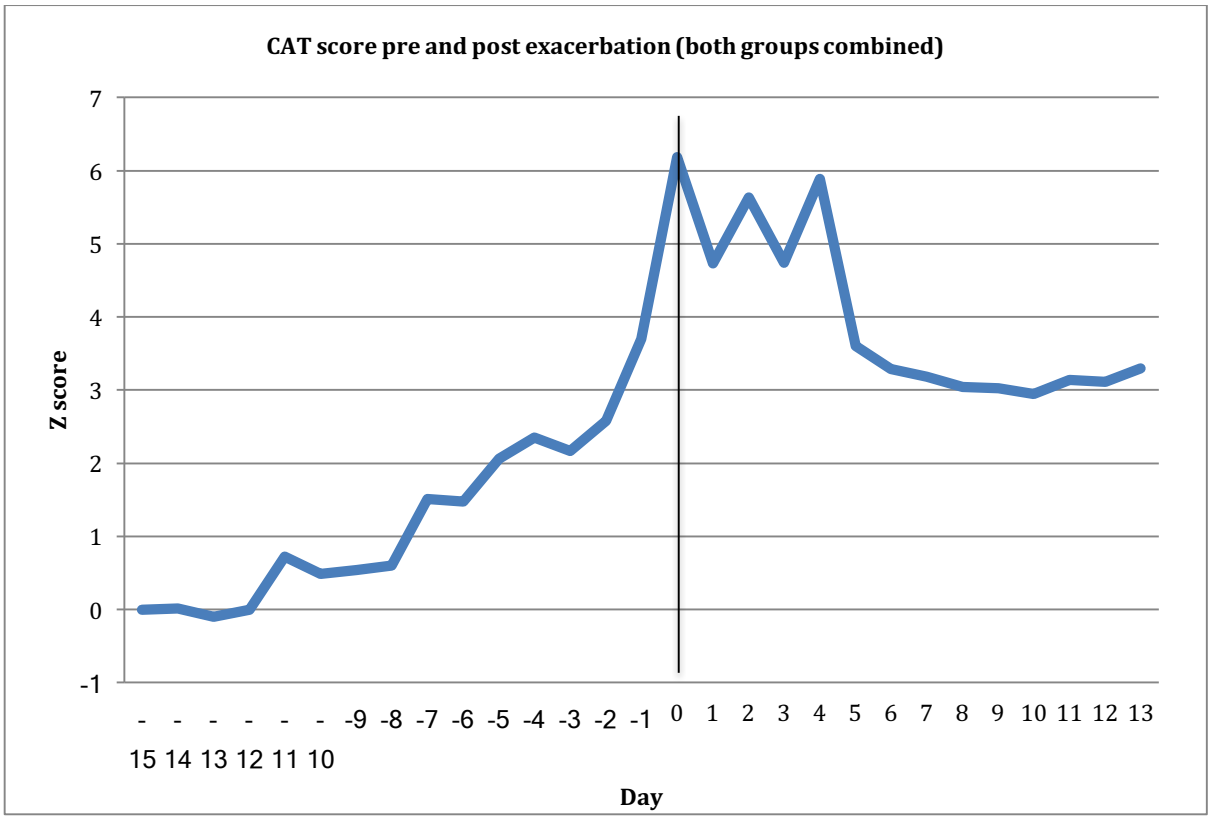

Figure 18. The CAT score pre-and-post exacerbation for the 27 COPD patients. The Y-axis represents the 95%CI of the baseline mean value. The X-axis represents the time expressed as days. Day -15 is the mean of the stable period, day -1 to day -14 is the pre-event period, day 0 is the day of exacerbation treatment, and day 0 to day 13 is the post-event period.

The Minimal Clinically Important Difference (MCID) for CAT questionnaire is two points. The mean CAT score for the 27 COPD patients increased above the MCID (more than two points) from day -5 to day 12 (Table 11). The difference in mean CAT score between the three phases was statistically

significant (stable= 15.6 points, pre= 17.4 points, post= 19.7 points) ($p<0.001$). Thus, patients had statistically and clinically elevated CAT scores from five days prior to treatment to at least 13 days following treatment. From this, we concluded that the exacerbations we detected were associated with significant changes in symptoms.

Table 11. Change in CAT score at Exacerbation of COPD.

Variable	Day	Once-daily group	Overnight group	Both groups combined
Mean CAT score	-15 (Baseline)	14.9	16.3	15.6
	-14	15.1	16.2	15.7
	-13	14.6	16.1	15.4
	-12	14.3	16.3	15.4
	-11	14.9	16.4	15.8
	-10	14.0	17.3	15.8
	-9	14.4	15.2	14.8
	-8	15.1	17.1	16.1
	-7	15.5	18.3	17.0
	-6	16.6	18.2	17.5
	-5	17.5	19.0	18.3
	-4	18.1	20.3	19.2
	-3	17.2	19.7	18.3
	-2	17.5	20.1	18.7
	-1	19.1	21.8	20.3
	0	22.0	23.1	22.6
	1	21.4	22.7	22.2
	2	23.7	22.5	23.1
	3	23.1	20.8	21.9
	4	20.9	21.2	21.1
	5	18.5	20.6	19.6
	6	18.0	20.1	19.0
	7	17.4	19.9	18.5
	8	17.1	19.1	18.0
	9	17.3	18.6	17.9
	10	17.5	18.0	17.7
	11	18.0	19.4	18.6
	12	17.9	18.6	18.2
	13	17.7	17.3	17.5

Red CAT scores are the scores increased above MCID.

Next, we wanted to assess whether exacerbations in the two randomised groups were similar (Figure 19). They appeared dissimilar. Although both were consistently increased, the overnight group crossed the threshold of 1.96SD earlier, peaked lower and recovered to baseline more quickly, whereas the once-daily group crossed the threshold later, peaked higher and remained symptomatic for longer.

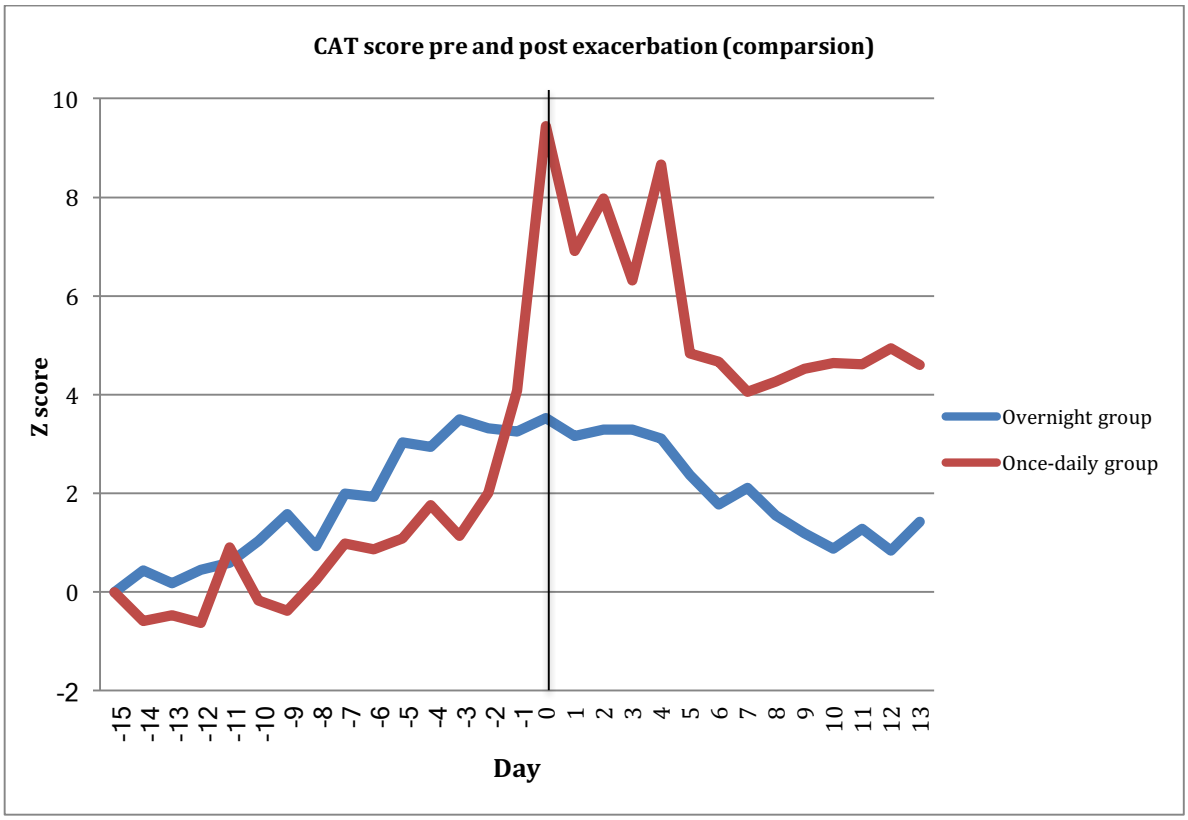

Figure 19. CAT score pre-and-post exacerbation for each group individually. The blue line represents the overnight (experimental) group, and the red line represents the once-daily (control) group. The Y-axis represents the 95%CI of the baseline mean value. The X-axis represents the time expressed as days. Day -15 is the mean of the stable period, day -1 to day -14 is the pre-event period, day 0 is the day of exacerbation treatment, and day 0 to day 13 is the post-event period.

Next, we looked in more detail at the symptom change in each group separately. The mean (SD) CAT score for the once-daily (control) group during the stable phase was 15.5 (±0.6) points. Figure 20 below shows that CAT was gradually increasing over time until it crossed the threshold

(>1.96SD away from the stable mean). The mean baseline value was greater than 1.96SD from day -2 to day 13. The CAT score increased above the MCID from day -4 to day 13 (Table 11). The difference in mean between the three different phases was statistically significant (p<0.001) with post hoc differences between the post-phase (19.2 points) versus the stable-phase (15.5 points, p<0.001), and the post-phase versus the pre-phase (16.7 points, p=0.001).

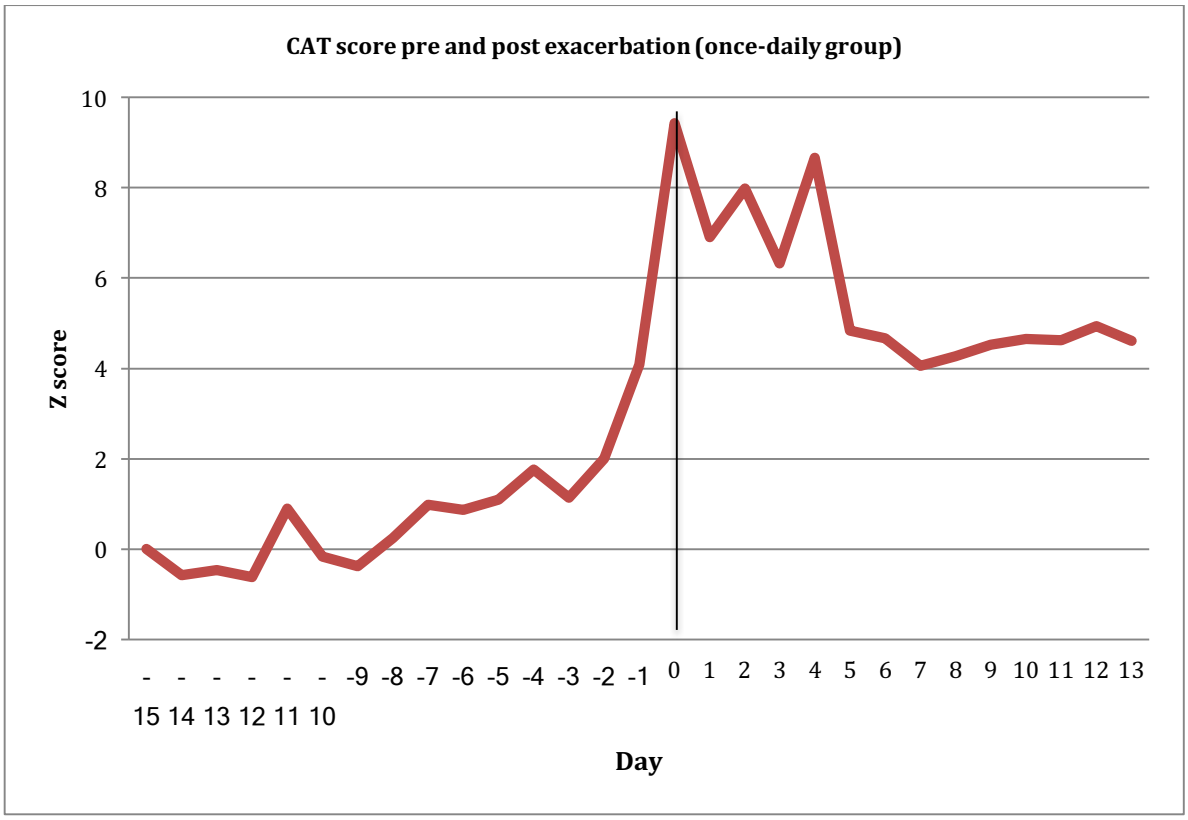

Figure 20. The CAT score pre-and-post exacerbation for the once-daily (control) group. The Y-axis represents the 95%CI of the baseline mean value for 14 patients. The X-axis represents the time expressed as days. Day -15 is the mean of the stable period, day -1 to day -14 is the pre-event period, day 0 is the day of exacerbation treatment, and day 0 to day 13 is the post-event period.

The mean (SD) CAT score for the overnight (experimental) group during the stable phase was 15.8 (±0.7) points. Figure 21 shows that CAT was gradually increasing overtime and crossed the threshold from day -7 until day 5. Moreover, the mean of the CAT score increased more than two points from day –7 to day 12 (Table 11). The difference in mean between the three different phases was statistically significant (stable= 15.8 points, pre= 18.0 points, post =20.3 points) ($p<0.001$).

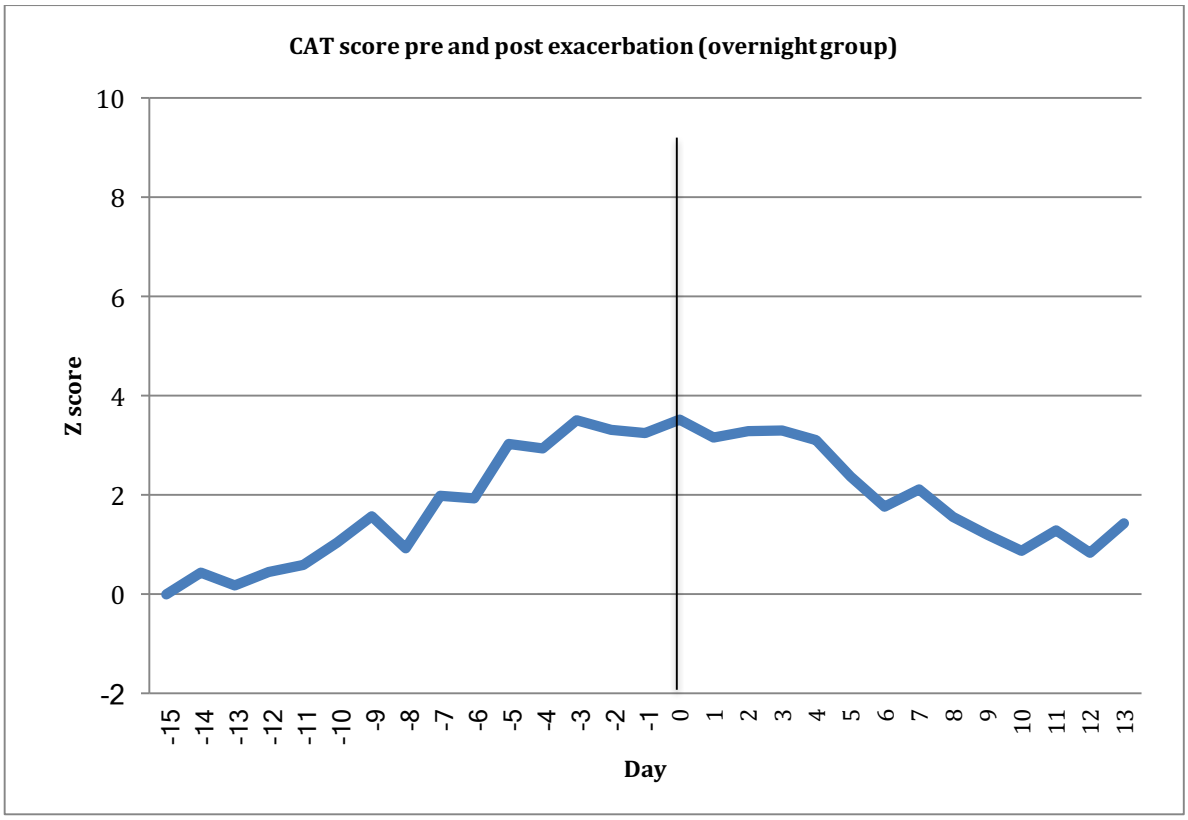

Figure 21. The CAT score pre-and-post exacerbation for the overnight (experimental) group. The Y-axis represents the 95%CI of the baseline mean value for 13 patients. The X-axis represents the time expressed as days. Day -15 is the mean of the stable period, day -1 to day -14 is the pre-event period, day 0 is the day of exacerbation treatment, and day 0 to day 13 is the post-event period.

6.3.3 Peak expiratory flow

Next, we looked at changes in peak expiratory flow to examine if changes in symptoms were associated with changes in respiratory physiology, rather than being due, for example, to anxiety. From the published literature we expected to see small changes in PEF through the time-course of exacerbation. The mean (SD) peak expiratory flow for the 27 COPD patients (both groups) at baseline was 214 (±3.7) L min^{-1}. As illustrated in Figure 22, the peak expiratory flow decreased gradually over time and dropped below 1.96SD in day 0 to day 4, with the maximal change at day 1.

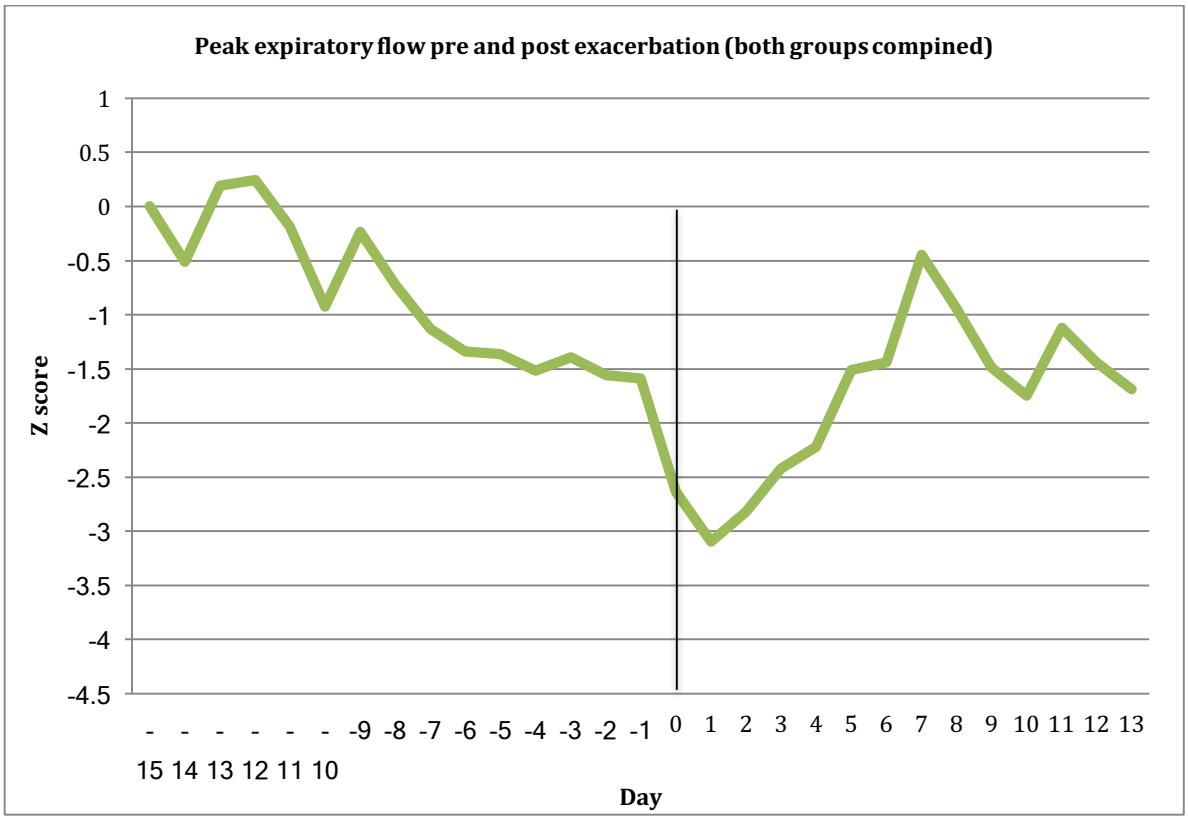

Figure 22. The peak flow measures pre-and-post exacerbation for the 27 COPD patients. The Y-axis represents the 95%CI of the baseline mean value. The X-axis represents the time expressed as days. Day -15 is the mean of the stable period, day -1 to day -14 is the pre-event period, day 0 is the day of exacerbation treatment, and day 0 to day 13 is the post-event period.

ANOVA testing showed a statistically (but not clinically) significant difference between the three different phases (stable= 213.8 L min^{-1}, pre= 201.6 L min^{-1}, post= 198.0 L min^{-1}) (p=0.001). The difference was noted between the stable phase (213.8 L min^{-1}) versus pre (201.6 L min^{-1}, p=0.016) and post (198 L min^{-1}, p<0.002) phases. Next, we looked at each group individually (Figure 23). Again, the exacerbations appeared dissimilar between the two groups.

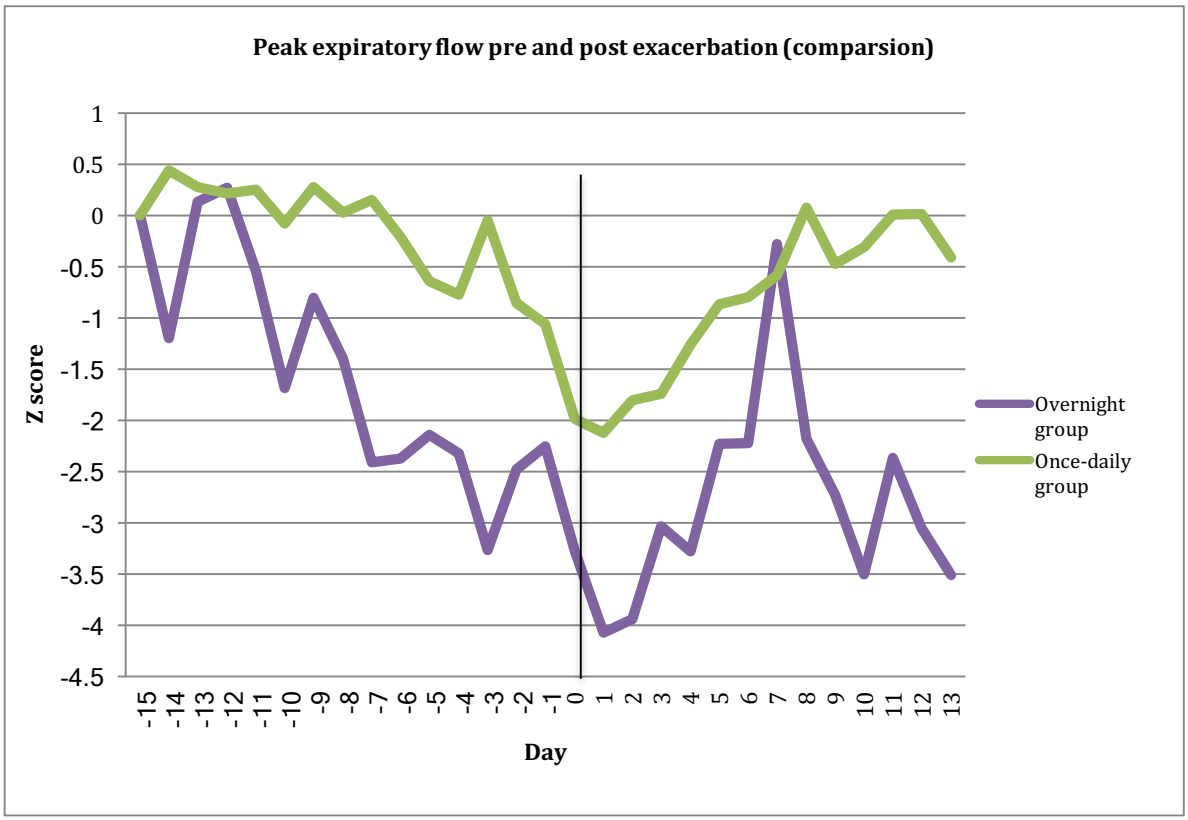

Figure 23. The peak flow pre-and-post exacerbation for each group individually. The purple line represents the overnight (experimental) group, and the green line represents the once-daily (control) group. The Y-axis represents the 95%CI of the baseline mean value. The X-axis represents the time expressed as days. Day -15 is the mean of the stable period, day -1 to day -14 is the pre-event period, day 0 is the day of exacerbation onset, and day 0 to day 13 is the post-event period.

The mean (SD) peak expiratory flow of the once-daily (control) group during the stable phase was 220.3 (±9.7) L min^{-1}. Figure 24 below shows that peak expiratory flow was gradually decreasing over time until it crossed the threshold of <1.96SD away from the stable mean. Peak expiratory flow decreased below 1.96SD from day 0 to day 1. The difference in mean between the three different phases (stable 220.3 L min^{-1}, pre 207.6 L min^{-1}, post 202.9 L min^{-1}) was statistically significant (p=0.016) with a difference between the stable-phase and the post-phase (p=0.016).

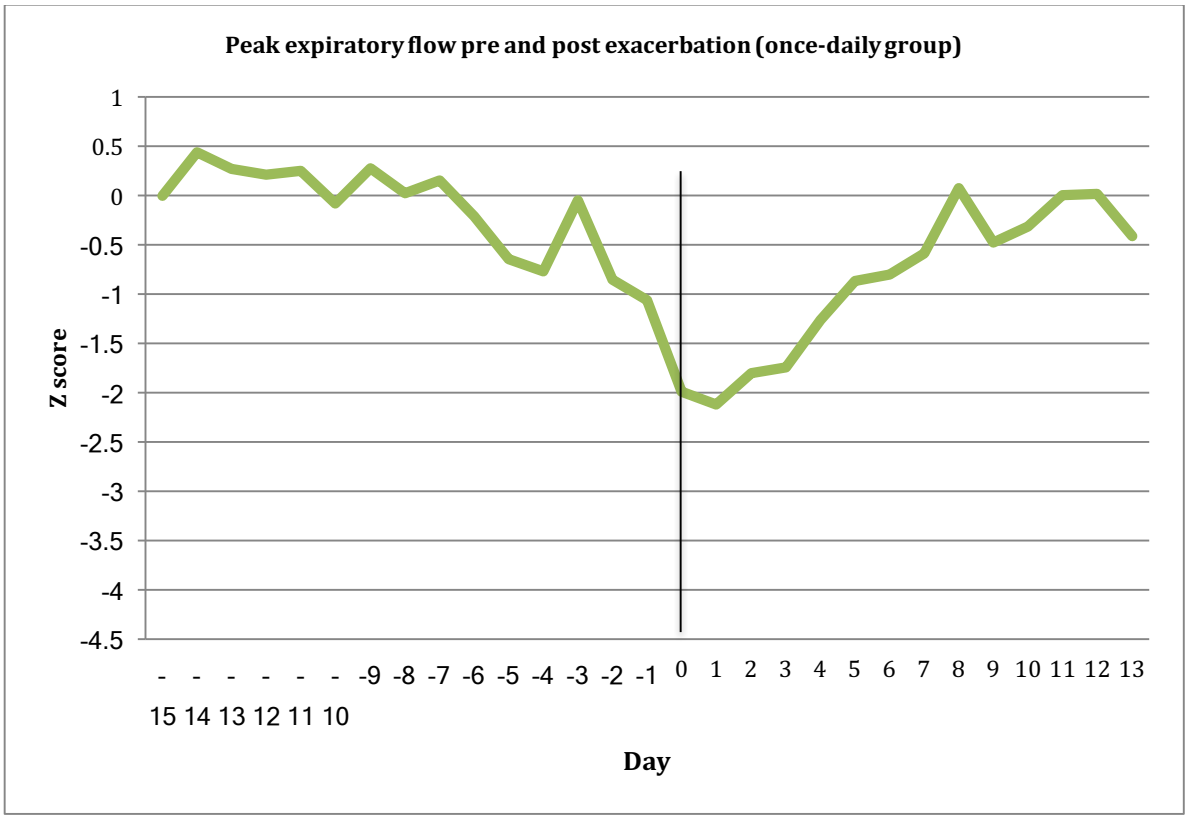

Figure 24. The peak flow measures pre-and-post exacerbation for the once-daily (control) group. The Y-axis represents the 95%CI of the baseline mean value for 14 patients. The X-axis represents the time expressed as days. Day -15 is the mean of the stable period, day -1 to day -14 is the pre-event period, day 0 is the day of exacerbation treatment, and day 0 to day 13 is the post-event period.

Figure 25 below shows the peak expiratory flow for the overnight (experimental) group pre-and-post exacerbation. The mean (SD) peak expiratory flow was 207.4 (±9.5) L min^{-1}. The overnight group crossed threshold (<1.96SD) from day -7 to day 13 (except in day 7). ANOVA test was performed but this did not show a statistically significant difference between stable= 207.4 L min^{-1}, pre= 195.6 L min^{-1}, and post= 192.4 L min^{-1} phases (p=0.052).

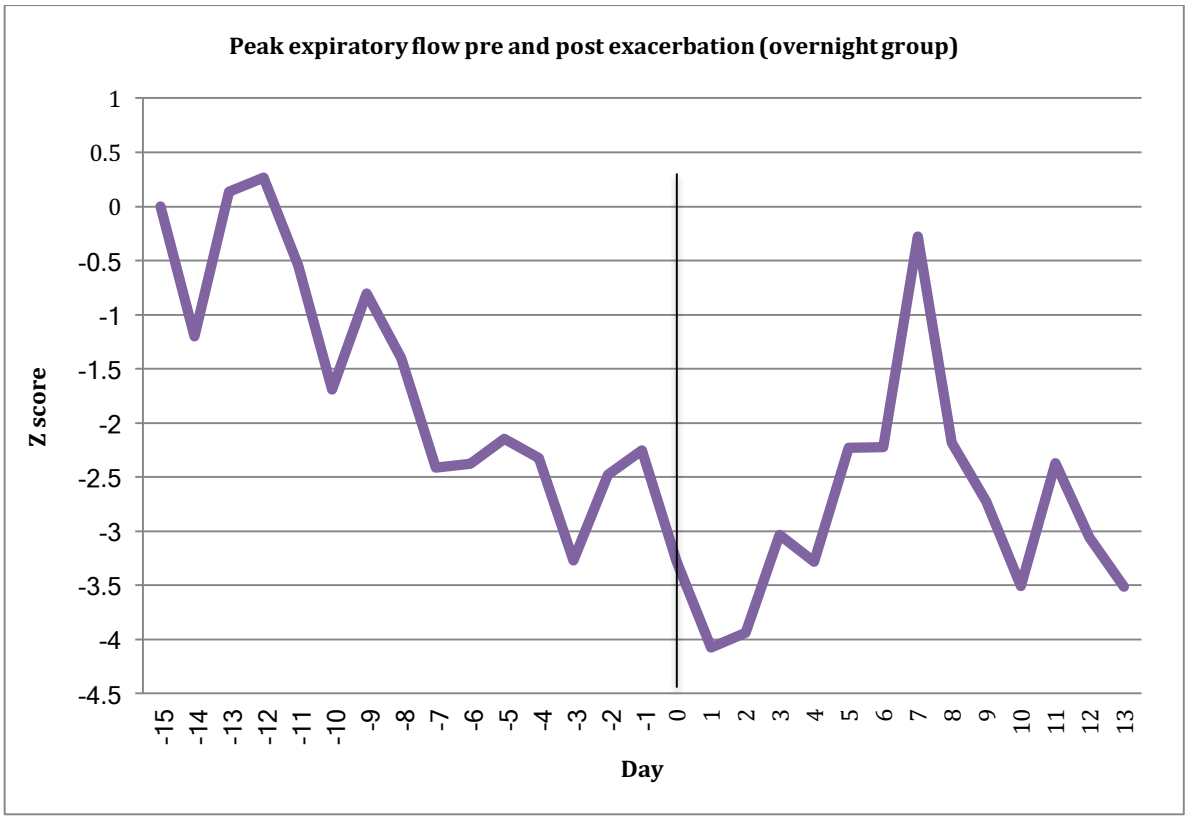

Figure 25. Peak flow measures pre-and-post exacerbation for the overnight (experimental) group. The Y-axis represents the 95%CI of the baseline mean value for 13 patients. The X-axis represents the time expressed as days. Day -15 is the mean of the stable period, day -1 to day -14 is the pre-event period, day 0 is the day of exacerbation treatment, and day 0 to day 13 is the post-event period.

In summary, the exacerbations we captured are associated with symptoms and PEF changes and therefore we consider them clinically significant. Exacerbations were somewhat dissimilar between the two groups with more

acute, more severe and more persistent changes in symptoms, but less severe and more rapidly resolving changes in PEF in the once-daily (control) group compared to the overnight monitoring group. We next went on to examine changes in the variables monitored differently between the groups.

6.3.4 Heart rate

Heart Rate is the first variable that was measured differently between the two randomised groups. The measures of heart rate in the once-daily group were taken once per day, whereas the measures of heart rate in the overnight group was taken continuously overnight (one measure every four seconds). Figure 26 below shows the once-daily (control) group (n=14) heart rate measures from two weeks before (day -1 to day -14) the exacerbation onset (day 0: start of treatment) and two weeks after (day 0 to day 13). Day -15 on the graph represents the stable period defined as the mean of two weeks measures of heart rate while the patients were stable. Changes in heart rate in the control group did not cross the threshold of 1.96SD.

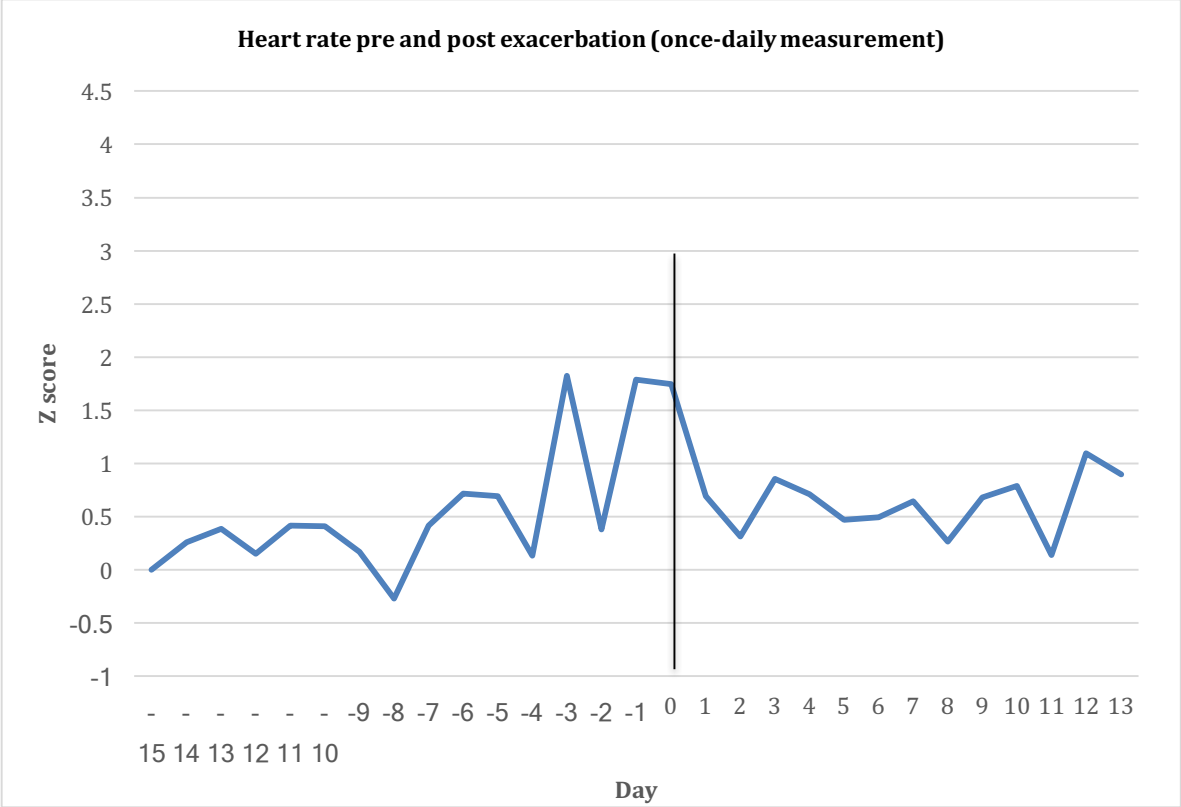

Figure 26. Heart rate measures pre-and-post exacerbation for the once-daily (control) group. The Y-axis represents the 95%CI of the baseline mean for 14 patients. The X-axis represents the time expressed as days. Day -15 is the mean of the stable period, day -1 to day -14 is the pre-event period, day 0 is the day of exacerbation treatment, and day 0 to day 13 is the post-event period.

The mean (SD) stable heart rate for the once-daily (control) group was 77.1 (±3.6) beats min^{-1}. The maximum change above the stable mean at day -1 (1.78SD) to day 0 (1.74SD) with a maximal increase of 7 beats min^{-1}, this increase was not statistically significant (P <0.05) – defined as crossing the threshold of >1.96SD away from the stable mean. An ANOVA test was applied and this did show a statistically (but not clinically) significant difference between the three different phases (stable= 77.1 beats $min^{-}1$, pre= 76.7 beats min^{-1}, post= 81.2 beats $min^{-}1$) P=0.007. The difference was seen between the post-phase (81.2 beats $min^{-}1$) versus stable phase (77.1

beats min-1, p=0.023), and the post-phase versus the pre-phase (76.7 beats min^{-1}, p=0.013).

Figure 27 below shows the trend of the heart rate for the overnight (experimental) group (n=13). The mean (SD) heart rate for the stable period was 70.0 (±1.8) beats min^{-1}. Compared to the once-daily (control) group, the SD was smaller (1.8/min vs. 3.6/min p<0.001); consequently, in the overnight group the heart rate crossed the threshold from day -7 (2.05SD) to day 2 (1.98SD) (consistently from day -5 to day 0) with a maximal increase of 10 beats min^{-1} (1.30SD). ANOVA testing showed a significant difference between the three phases (stable= 70.0 beats min^{-1}, pre= 73.9 beats min^{-1}, post= 67.6 beats min^{-1}) (p=0.001). The difference was between the pre-phase (73.9 beats min^{-1}) versus the stable (70.0 beats min^{-1}) and the post-phase (67.6 beats min^{-1}) with a p-value of p=0.037 and p=0.001 respectively.

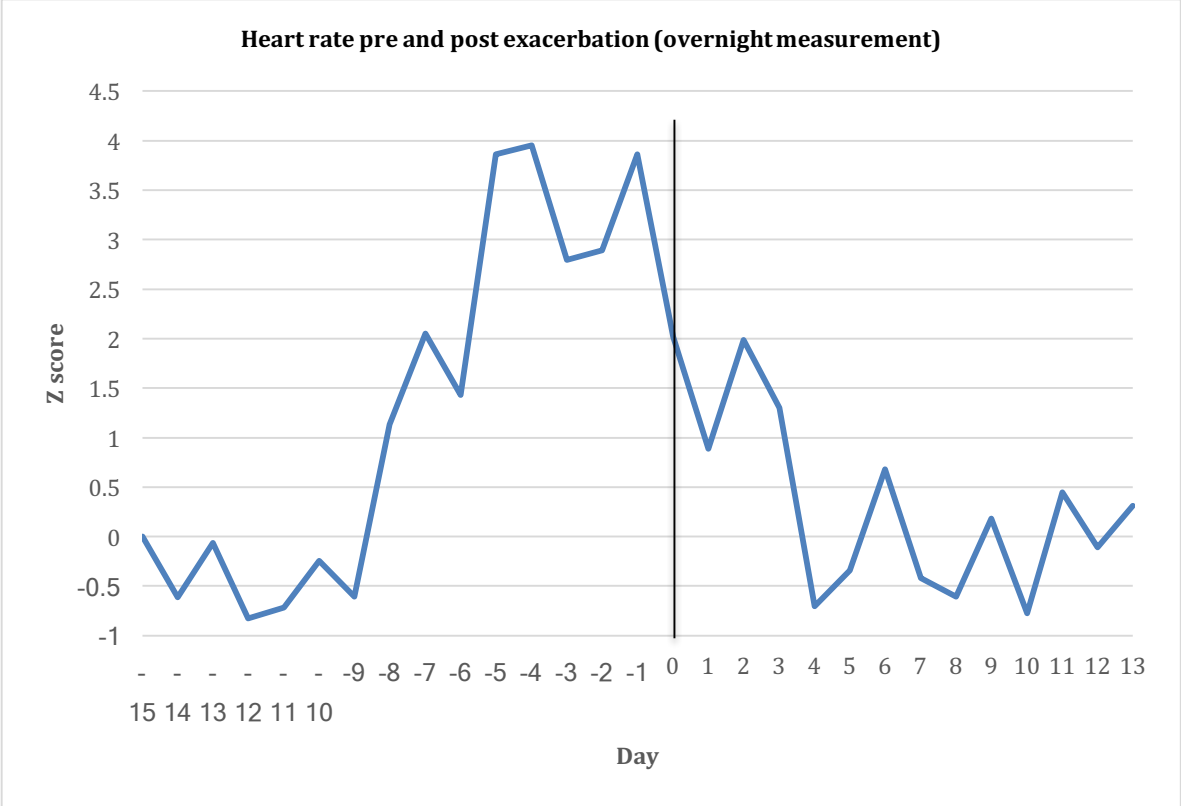

Figure 27. Heart rate measures pre-and-post exacerbation for the overnight (experimental) group. The Y-axis represents the 95%CI of the baseline mean for 13 patients. The X-axis represents the time expressed as days. Day -15 is the mean of the stable period, day -1 to day -14 is the pre-event period, day 0 is the day of exacerbation treatment, and day 0 to day 13 is the post-event period.

6.3.5 Oxygen saturation (SpO_2%)

Next, we looked at the trend of oxygen saturation and examined the variation pre-and post- exacerbation. Figure 28 below shows the SpO_2% variability for the control group pre- and post- exacerbation. The mean (SD) oxygen saturation during the stable period for those 14 patients was 94.0 (±0.81) %. Any measure below by >1.96SD away from the stable mean would therefore be considered statistically significant.

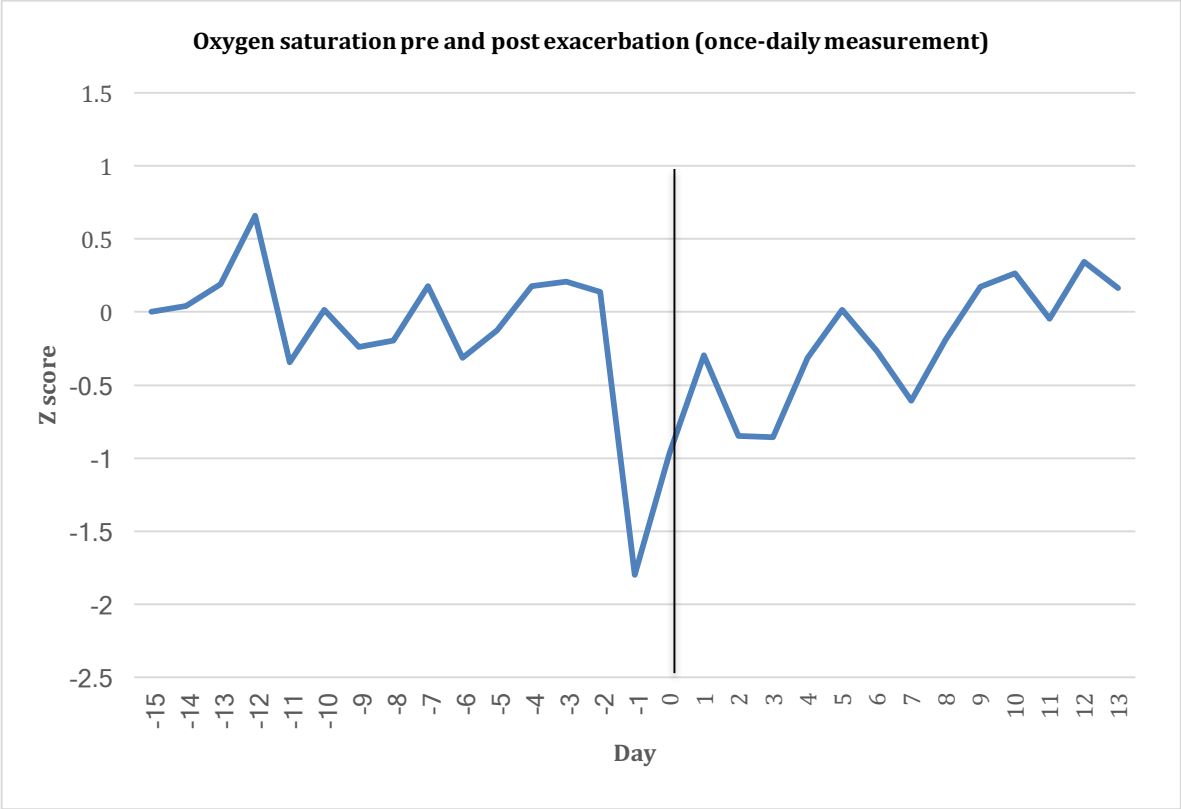

Figure 28. Oxygen saturation measures pre- and post-exacerbation for the once-daily (control) group. The Y-axis represents the 95%CI of the baseline mean for 14 patients. The X-axis represents the time expressed as days. Day -15 is the mean of the stable period, day -1 to day -14 is the pre-event period, day 0 is the day of exacerbation treatment, and day 0 to day 13 is the post-event period.

Figure 28 shows that the SpO_2% variability was generally within the stable range (±0.81) with a maximum fall of -1.80SD at day -1 (with a maximal

mean fall of 2%) An ANOVA test showed no difference between the three different phases (stable= 94.0%, pre= 93.9%, post= 93.2%) (p= 0.090).

Figure 29 shows the SpO_2% for the overnight (experimental) group. The mean (SD) oxygen saturation for the stable phase was 91.0 (±0.36). Compared to the once-daily (control) group, the SD was smaller (0.36 vs. 0.81% p= 0.002). The SpO_2% decreased for more than 1.96SD on three days: -7, -6, and -1 (-1.93SD, -2.04SD, -2.25SD) respectively, with a maximal mean fall of 1.2% but these changes did not occur over a consistent period. The mean of the three phases (stable= 91.0%, pre= 91.0, post= 91.3%) did not show any statistically significant difference (p=0.258).

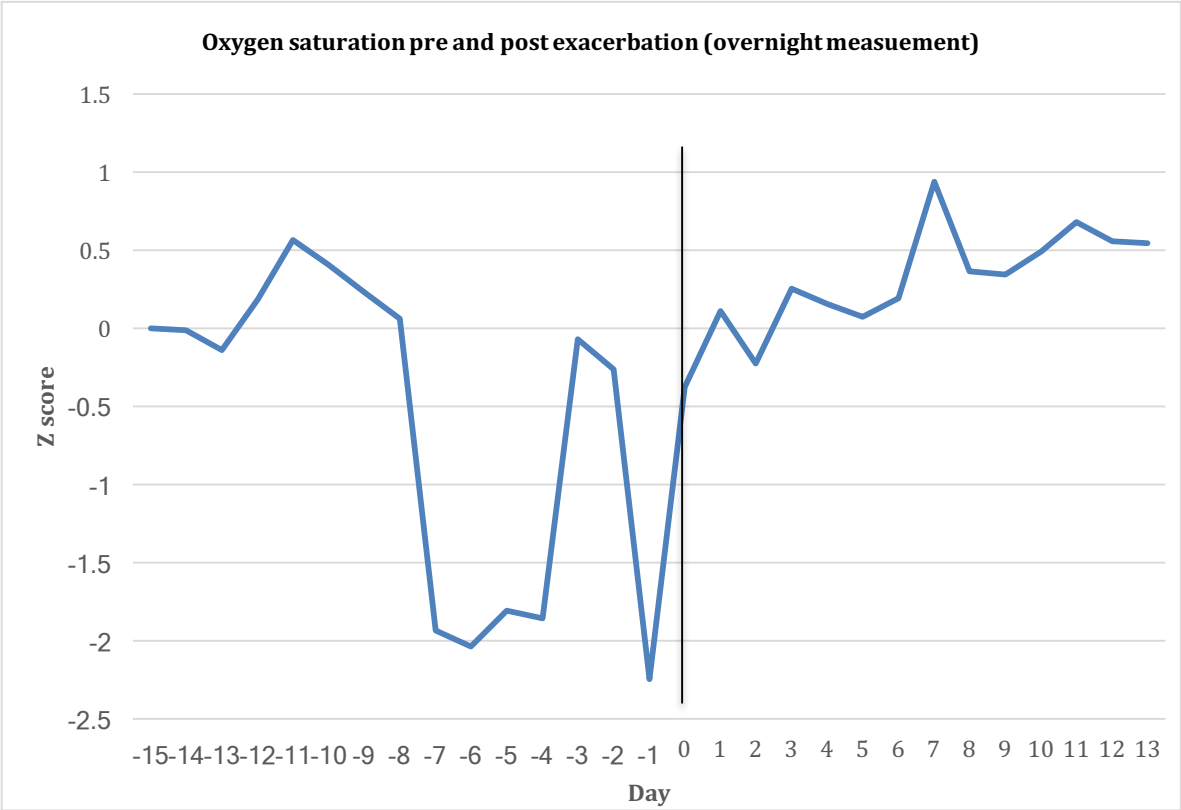

Figure 29. The overnight oxygen saturation measures pre- and post- exacerbation for the overnight (experimental) group. The Y-axis represents the 95%CI of the baseline mean for 13 patients. The X-axis represents the time expressed as days. Day -15 is the mean of the stable period, day -1 to day -14 is the pre-event period, day 0 is the day of exacerbation treatment, and day 0 to day 13 is the post-event period.

SUMMARY TABLE

Table 12. Summary table of the days where variables showed statistically significant variation from baseline.

Variable	Once-daily group	Overnight group	Combined groups
CAT score	From day -2 to day 13 P<0.001	From day -7 to day 5 P<0.001	From day -5 to day 13 P<0.001
Peak expiratory flow	From day 0 to day 1 p=0.016	From day -7 to day 13 P=0.052	From day 0 to day 4 p=0.001
Heart rate	None p=0.007	Day -7, -5, -4, -3, -2, -1, 0, and day 2 P=0.001	-
Oxygen saturation	None p=0.090	Day -7, -6, and day -1 P=0.258	-

p-value * is the difference of means for the three different phases (stable, pre, post)

6.3.6 Correlation between symptoms and physiological variables

We next examined the relationship between the severity of symptoms and changes in physiological variables pre and post- exacerbation. The

correlation between variables was assessed only during periods patients were not at baseline (pre- and post-exacerbation combined and separately) (Table 13). In this exploratory analysis (not corrected for statistical multiplicity), correlation tests were applied six times for each group: 1) two weeks pre and post-exacerbation combined, 2) two weeks only pre-exacerbation, 3) two weeks only post-exacerbation, 4) one week pre- and post-exacerbation combined, 5) one week only pre-exacerbation, and 6) one week only post-exacerbation.

Table 13. Correlations between monitored variables (symptoms (CAT questionnaire), peak expiratory flow (PEF), heart rate (HR), and oxygen saturation (Sat). Six different periods are presented in this table pre- and post-exacerbation combined, and separately. The negative symbol (-) means there was no significant correlation noted.

Groups	Time (weeks)	CAT - PEF	CAT - HR	CAT – Sat	PEF - HR	PEF - Sat	HR - Sat
Once-daily	2 weeks (pre&post)	r= -0.687 p< 0.001	r= 0.580 p= 0.001		-	-	-
	2 weeks (pre only)	r= -0.655 p= 0.011	-	-	-	-	-
	2 weeks (post only)	r= -0.810 p< 0.001	-	-	-	-	-
	1 week (pre&post)	r= -0.861 p< 0.001	r= 0.710 p= 0.004	-	r= -0.585 p= 0.028	-	-
	1 week (pre only)	r= -0.893 p= 0.007	-	-	-	-	-
	1 week (post only)	r= -0.795 p= 0.033	-	r= 0.754 p= 0.050	-	-	-
Overnight	2 weeks (pre&post)	r= -0.469 p= 0.012	-	R= -0.430 p= 0.022	r= -0.530 p= 0.004	-	-
	2 weeks (pre only)	r= -0.554 p= 0.040	r= 0.919 p< 0.001	r= -0.701 p= 0.005	r= -0.676 p= 0.008	-	r= -0.694 p= 0.007
	2 weeks (post only)	r= -0.733 p= 0.003	r= 0.652 p= 0.012	-	-	-	-
	1 week (pre&post)	-	r= 0.613 p= 0.020	-	r= -0.835 p< 0.001	r= 0.559 p= 0.038	r= -0.666 p= 0.009
	1 week (pre only)	-	r= 0.905 p= 0.005	-	-	-	-
	1 week (post only)	-	-	-	-	-	-

In the once-daily measurement group, the greatest number of correlations between variables was observed when considering one week pre- and post-exacerbation data combined. CAT score showed a negative correlation with peak expiratory flow (r=-0.861, p<0.001; the greater the symptoms the lower the PEF) (Figure 30), and positive correlation with heart rate (r=0.710, p=0.004; the greater the symptoms the higher the heart rate) (Figure 31). In addition, heart rate showed a negative correlation with peak expiratory flow (r=-0.585, p<0.028) (Figure 32). We therefore conclude that physiological variables such as HR and PEF are reflecting exacerbation severity as assessed by symptom (CAT) severity.

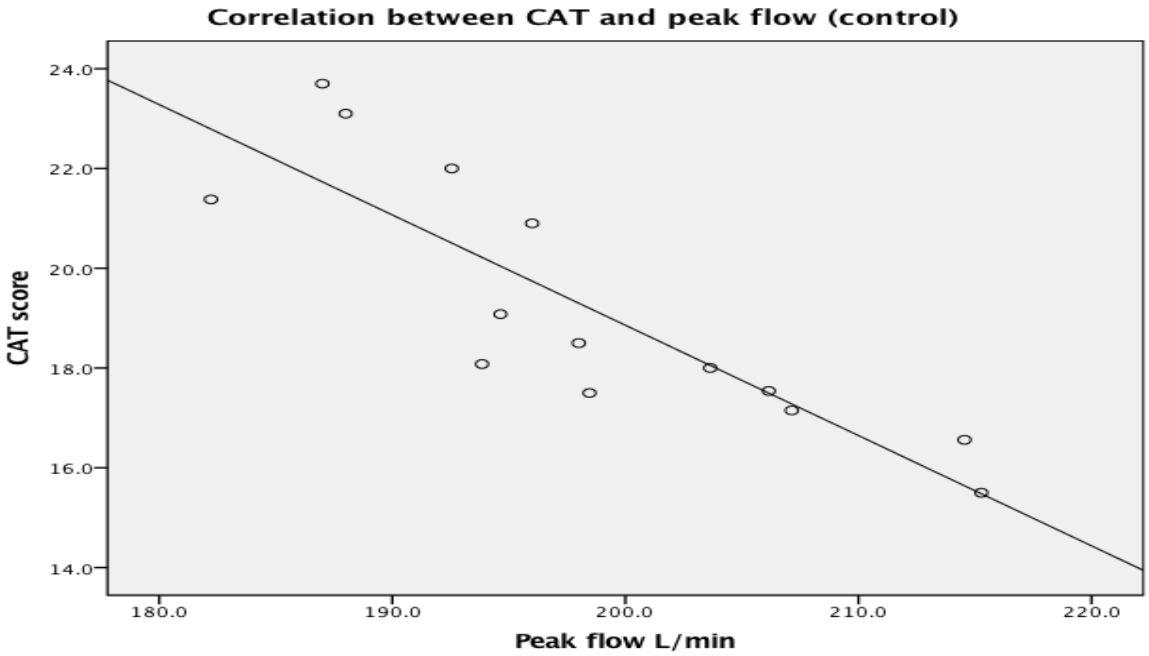

Figure 30. The correlation between CAT score and peak flow L min^{1} for the once-daily (control) group in the one week pre-and-post exacerbation period. The X-axis represents the peak flow L min^{1}, and the Y-axis represents the CAT score points.

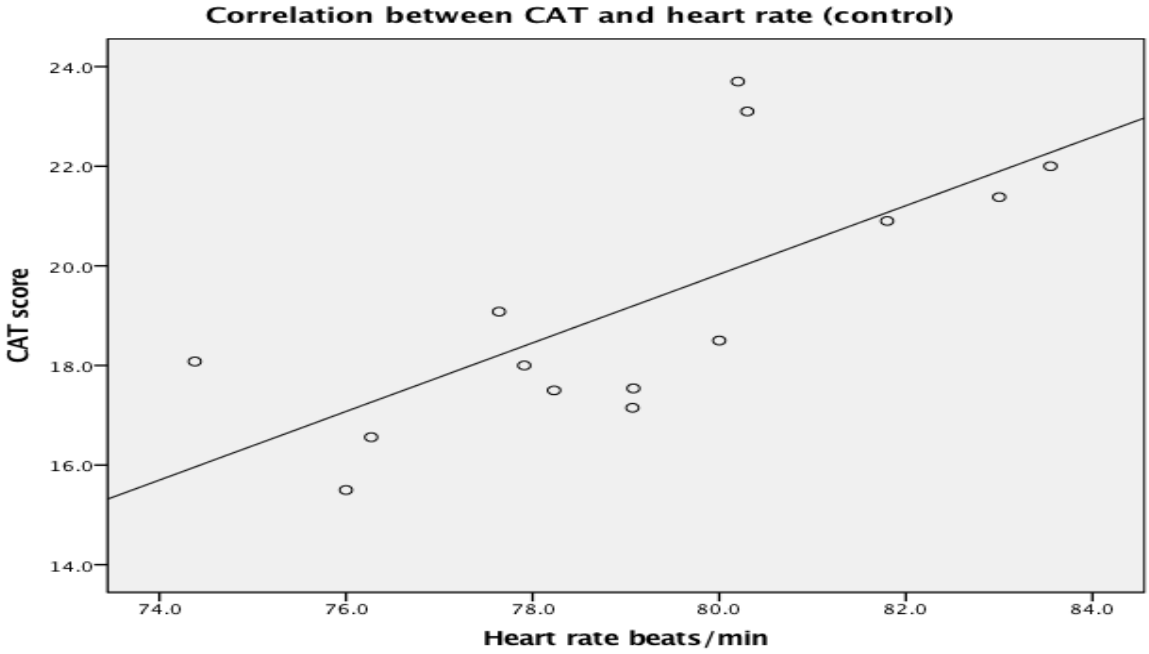

Figure 31. The correlation between the CAT score and heart rate for the once-daily (control) group in the one week pre- and post-exacerbation period. The X-axis represents the heart rate beats min^{1}, and the Y-axis represents the CAT score.

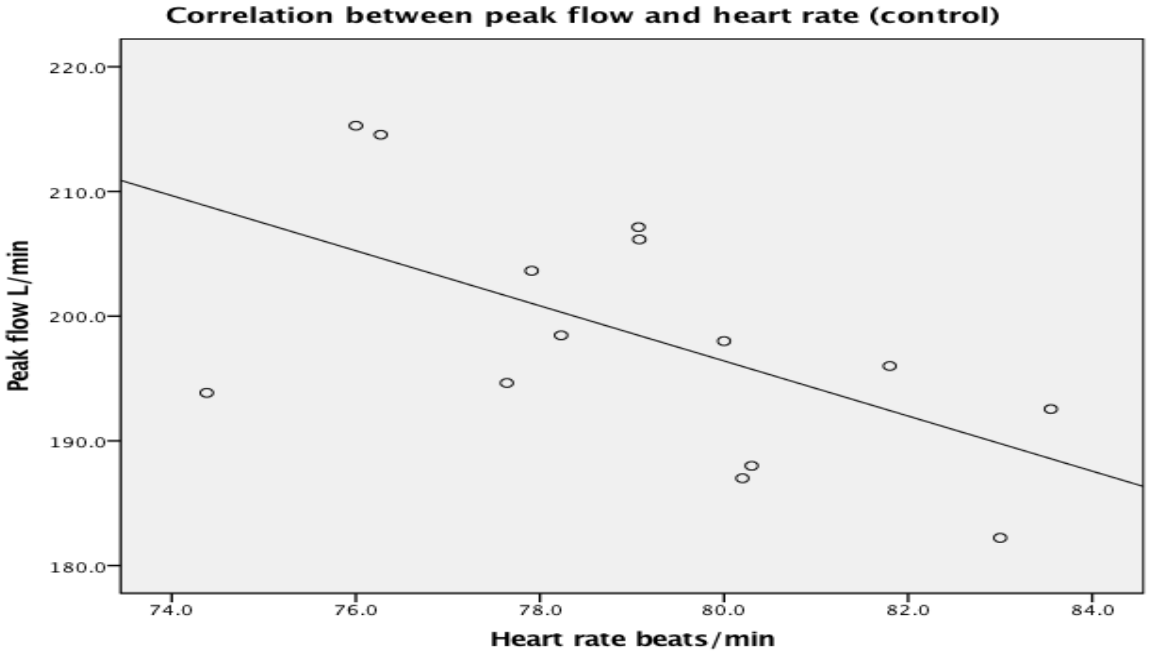

Figure 32. Correlation between peak flow (L min^{1}) and heart rate (beats min^{1}) for the once-daily (control) group in the one week pre- and post-exacerbation period. The X-axis represents the heart rate, and the Y-axis represents the peak flow.

There were also statistically significant correlations between symptom severity (CAT) with physiological variables in the overnight monitoring group. In general, there were more correlations observed in the overnight monitoring group, suggesting a closer link between symptoms and physiology when physiology is measured overnight. Variables were correlated most in the two weeks pre-exacerbation, and one week pre-and-post exacerbation data (Table 13). The correlation in the overnight group in the two weeks only pre-exacerbation showed that CAT score was negatively correlated with peak expiratory expiratory flow ($r= -0.554$, $p= 0.040$) (Figure 33), and positively correlated with heart rate ($r= 0.919$, $p<0.001$) (Figure 34). Moreover, heart rate was negatively correlated with peak expiratory flow ($r=-0.676$, $p=0.008$) (Figure 35), and oxygen saturation ($r=-0.694$, $p=0.007$) (Figure 36). Oxygen saturation was negatively correlated with CAT ($r=-0.701$, $p=0.005$) (Figure 37).

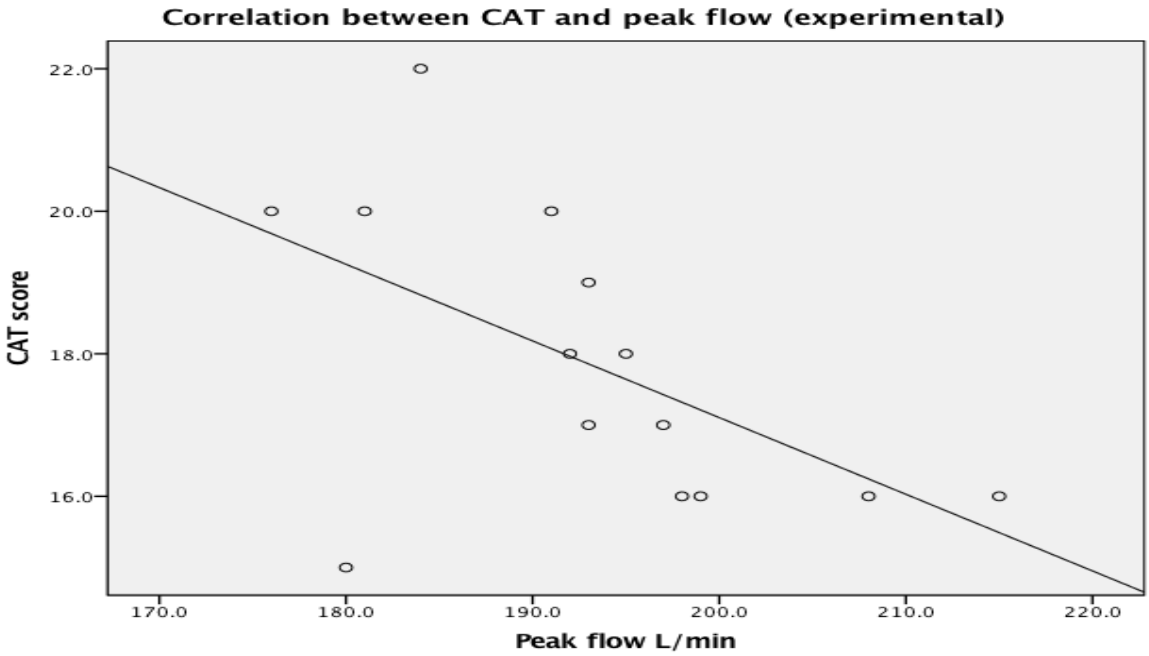

Figure 33. Correlation between CAT score and peak flow L min^{1} for the overnight (experimental) group in the two weeks pre-exacerbation period. The X-axis represents the peak flow L min^{1}, and the Y-axis represents the CAT score.

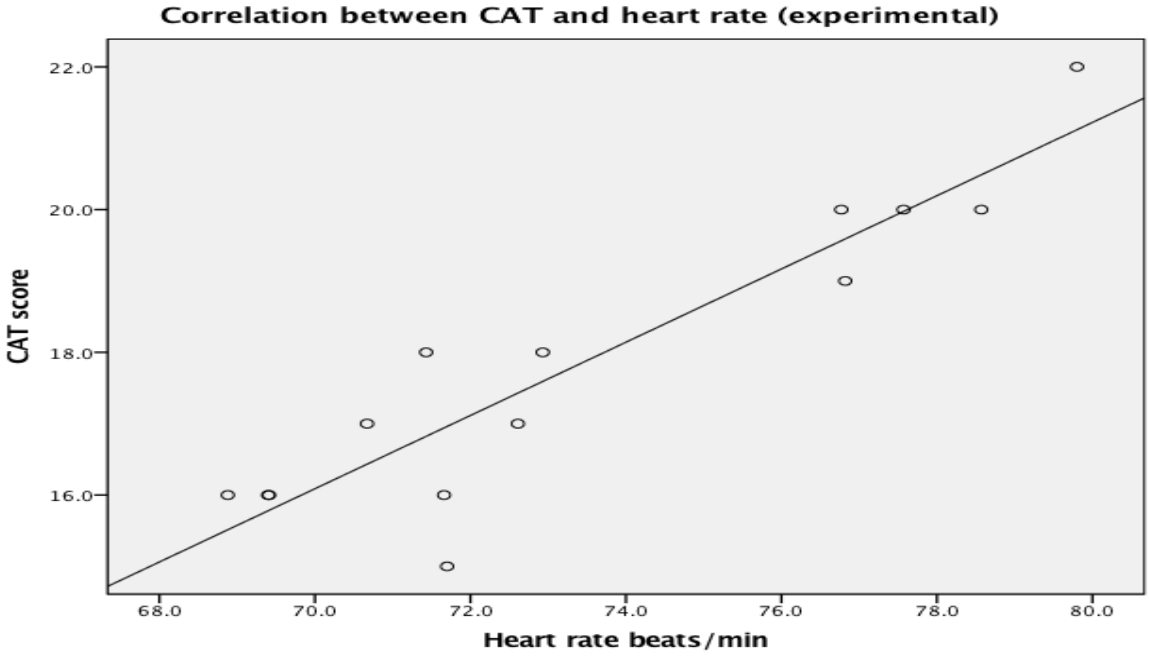

Figure 34. Correlation between CAT score and heart rate for the overnight (experimental) group in the two weeks pre-exacerbation. The X-axis represents heart rate beats min^{1}, and the Y-axis represents the CAT score.

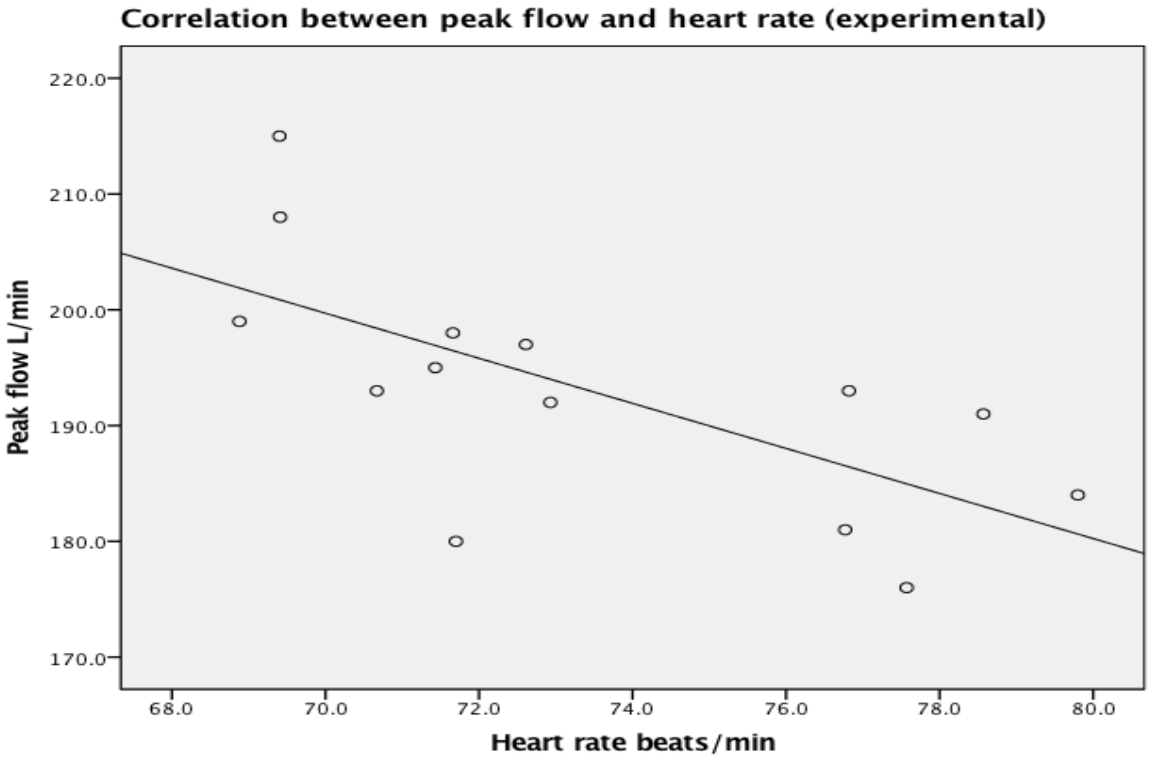

Figure 35. Correlation between peak flow and heart rate for the overnight (experimental) group in the two weeks pre-exacerbation period. The X-axis represents the heart rate beats min^{1}, and the Y-axis represents peak flow L min^{1}.

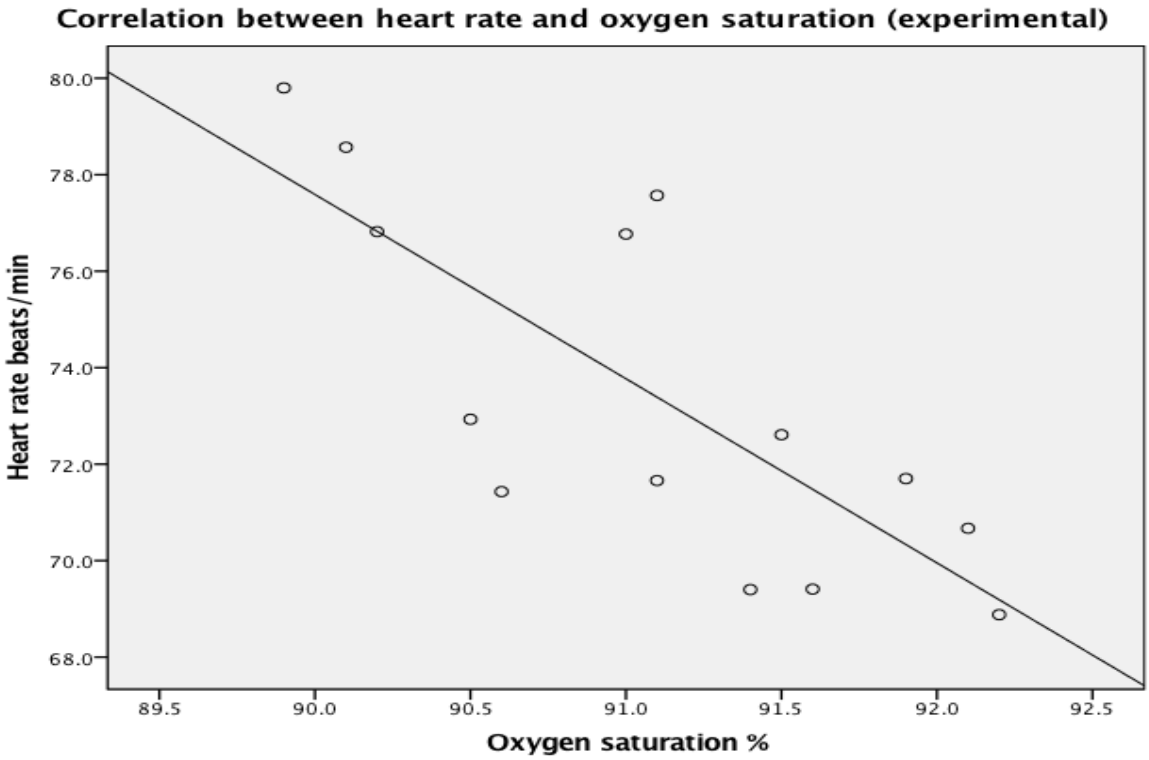

Figure 36. Correlation between heart rate and oxygen saturation for the overnight (experimental) group in the two weeks pre-exacerbation period. The X-axis represents the oxygen saturation %, and the Y-axis represents the heart rate beats min^{1}.

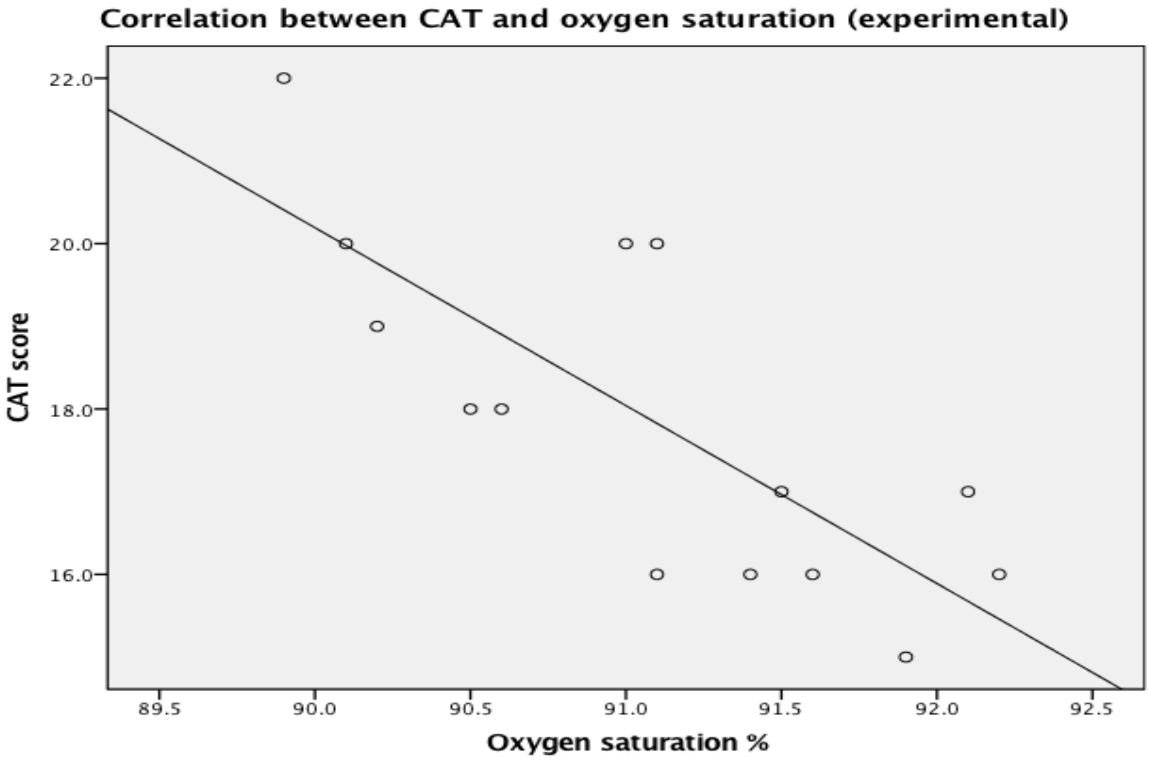

Figure 37. Correlation between CAT score and oxygen saturation for the overnight (experimental) group in the two weeks pre-exacerbation period. The X-axis represents the oxygen saturation %, and the Y-axis represents the CAT score.

Both groups in this study were asked to take measures of their peak expiratory flow daily; therefore, the correlation of CAT score with peak expiratory flow for the 27 COPD patients was also assessed (Table 14). Peak expiratory flow was correlated in all the periods except for the "one week pre-exacerbation" data. The relation between the two variables was negative in all periods, such that greater symptoms was associated with lower PEF. The period of "two weeks only pre-exacerbation" ($r= -0.700$, $p<0.001$), and "two weeks only post-exacerbation" showed strongest correlations ($r= -0.823$, $p<0.001$) (Figure 38).

Table 14. Correlation between symptoms (CAT questionnaire) and peak expiratory flow. Six different periods are presented in this table pre- and post-exacerbation combined, and separated. The negative symbol (-) means there was no significant correlation noted.

Groups	Time (weeks)	CAT - PEF
Once-daily and overnight (combined)	2 weeks (pre & post)	r= -0.674 p<0.001
	2 weeks (pre only)	r= -0.700 p<0.001
	2 weeks (post only)	r= -0.823 p<0.001
	1 week (pre & post)	r= -0.479 p= 0.010
	1 week (pre only)	-
	1 week (post only)	r= -0.680 p= 0.007

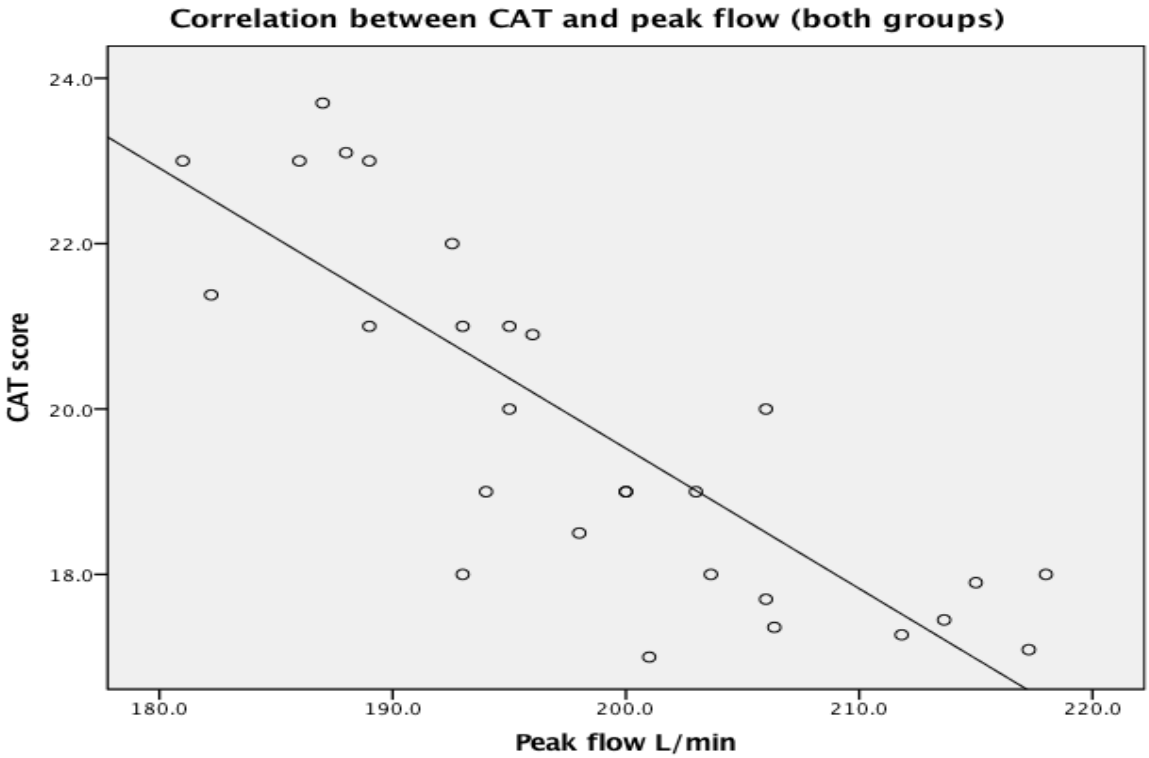

Figure 38. Correlation between CAT score and peak flow for the once-daily and overnight (control and experimental) groups in the two weeks post-exacerbation period. The X-axis represents the peak flow L min^{1}, and the Y-axis represents the CAT score.

6.3.7 Time difference to exacerbation between symptoms and physiology

Our primary analysis was to assess the time difference in days to receive treatment from the day where a change was first observed to be statistically different compared to baseline (>1.96SD away from the stable mean) between symptoms (CAT questionnaire) and physiological variables (PEF, HR, and SpO_2%). First, we combined both groups to assess the difference in time between symptoms and peak expiratory flow (n=27). The median (IQR) time to receive treatment from symptoms becoming abnormal was -2.0 (-10.0 – 0.0) days, whilst for peak expiratory flow it was -0.5 (-5.3 – 0.0) days (p=0.147). Next, the same analysis was applied to each group individually to examine if there was any difference between symptoms and physiology, and if there was any difference between overnight measurement and once-daily measurement. In the once-daily measurement group, there were no significant differences noted between symptoms and physiological variables nor within physiological variables (p>0.050) (Table 15).

Table 15. Time diffrence in days to receive treatment at exacerbation between symptoms and physiological variables first becoming abnormal.

Groups	CAT - PEF	CAT - HR	CAT – Sat	PEF - HR	PEF - Sat	HR - Sat
Once-daily	-1 (-9.0 – 0.0) vs 0.0 (-1.5 – 0.0) days p= 0.138	-1 (-9.0 – 0.0) vs 0.0 (-0.5 – 0.0) days p= 0.406	-1 (-9.0 – 0.0) vs 0.0 (-2.0 – 0.0) days p= 0.128	0.0 (-1.5 – 0.0) vs 0.0 (-0.5 – 0.0) days p= 0.725	0.0 (-1.5 – 0.0) vs 0.0 (-2.0 – 0.0) days p= 0.666	0.0 (-0.5 – 0.0) vs 0.0 (-2.0 – 0.0) days p= 0.866
Overnight	-5.0 (-11.0 – 0.0) vs -5.0 (-8.0 – 0.0) days p= 0.476	-5.0 (-11.0 – 0.0) vs -5.0 (-7.5 – -0.5) days p= 0.779	-5.0 (-11.0 – 0.0) vs 0.0 (-3.5 – 0.0) days p= 0.130	-5.0 (-8.0 – 0.0) vs -5.0 (-7.5 – -0.5) days p= 0.455	-5.0 (-8.0 – 0.0) vs 0.0 (-3.5 – 0.0) days p= 0.307	-5.0 (-11.0 – 0.0) vs 0.0 (-3.5 – 0.0) days p= 0.123

We also assessed the difference in time between symptoms and physiological variables becoming abnormal, and start of treatment, in the experimental group. Again, no significant differences were noted between the variables (p>0.050) (Table 15).

Finally, the difference in time between the two groups for all the variables was assessed. Among all the variables only heart rate showed a statistically significant difference in time to receive treatment between the overnight measurement group compared to the once-daily measurement group (median -5.0 (-7.5 – -0.5) days vs 0.0 (-0.5 – 0.0) days) (p=0.026), respectively (Table 16). This shows that overnight monitoring of heart rate has the greatest potential to detect, or assist in the detection of exacerbations of COPD and was better than once-daily measurement taken during the day.

Table 16. Time diffrence in days to receive treatment between once-daily measurment group and overnight measurment group.

Groups	CAT	HR	Oxygen sat	PEF
Once-daily vs overnight	-1 (-9.0 – 0.0) vs -5.0 (-11.0 – 0.0) p= 0.327	0.0 (-0.5 – 0.0) vs -5.0 (-7.5 – -0.5) p= 0.026	0.0 (-2.0 – 0.0) vs 0.0 (-3.5 – 0.0) p= 0.642	0.0 (-1.5 – 0.0) vs -5.0 (-8.0 – 0.0) p= 0.124

Discussion

We have conducted a randomised clinical trial to study the possibility of predicting a COPD exacerbation by monitoring patients' physiological parameters overnight, thus removing non-COPD related effects, for example, anxiety and exercise from the physiological signal. Our key findings are: the time difference to receive treatment between changes in symptoms and changes in physiology becoming abnormal were not statistically significant. There was a significant delay in patients' symptom scores changing and treatment commencing. There are correlations between symptom scores and physiological variables. Physiological parameters change significantly up to seven days before exacerbation onset. Overnight measurement of heart rate may permit earlier detection of exacerbation than once-daily measurement, likely because the standard deviation of the change is smaller and thus the ability to see real differences is larger. The findings of this study support our hypothesis that nocturnal recording and subsequent analysis of physiology could permit earlier detection of a COPD exacerbation, but it would appear that monitoring symptoms alone may be a better way to achieve this.

COPD exacerbation is defined by a change in respiratory symptoms above day-to-day variation (1). Seemungal et al. reported changes in respiratory symptoms from baseline in 101 COPD patients, noting symptoms changed significantly during the seven day period preceding the exacerbation (122). Further, Aaron et al. reported that the median (IQR) duration of change in symptoms in 44% of "gradual exacerbation pattern"

was 4 (2 – 8) days prior to the day of exacerbation (77). Our findings on 27 COPD exacerbations showed that symptoms were increased significantly above baseline up to five days before the day of exacerbation treatment (Figure 19). In our study, we used the CAT questionnaire to assess symptom severity. A previous study by Lee has investigated the use of the CAT questionnaire in the prediction of COPD exacerbations (153). Previous studies have shown that the CAT questionnaire is responsive to various interventions such as treatment and pulmonary rehabilitation (154, 155). Kon et al. in 2014 conducted three studies to identify the Minimal Clinically Important Difference (MCID) for the CAT questionnaire. They reported that a two point change in CAT score can be considered the MCID (156). Previous studies have shown that mean of CAT score rose above two points (MCID) from baseline at exacerbation onset (157). This is consistent with our findings as the mean CAT score in our study increased above baseline more than two points (MCID) five days before exacerbation onset (Table 11).

In our study, we monitored three physiological variables: peak expiratory flow, heart rate, and oxygen saturation. The evidence for using physiological parameters to identify exacerbations is controversial and under investigation. Our findings showed that for heart rate and PEF but not oxygen saturation the mean during the stable phase was significantly different from the mean during the pre-phase, suggesting that the variability of those parameters is changing as the patient becomes unwell (unstable). It also supports the hypothesis that COPD exacerbations affect physiological

parameters and those variables may facilitate the earlier identification of exacerbations.

Peak expiratory flow is a useful simple tool to assess lung function at home, and measurements of peak expiratory flow are correlated with FEV_1 (158, 159). The peak expiratory flow of 27 patients in our findings was decreasing gradually during the pre-phase and was significantly different from baseline at the day of exacerbation (Figure 22). The drop of peak expiratory flow of the 27 patients from baseline during the exacerbation was 34 L min^{-1}. We believe that a fall in peak expiratory flow during exacerbation would be expected as patients' airways become narrowed and obstructed due to bronchospasm, oedema, and mucus plugging, which lead to increased airway resistance. Seemungal et al. reported that peak expiratory flow in their study fell below baseline at exacerbation with a median (IQR) of 6.6 (0.0 – 16.6) L min^{-1} (160). Furthermore, in another study conducted by Seemungal et al. peak expiratory flow fell significantly from baseline at the day of exacerbation with a median (IQR) of 8.6 (0.0 – 22.9) L min^{-1} (122). Even though these changes are statistically significant, we believe that a fall in peak flow of this amount would not be clinically significant, and not measurable with current PEF devices.

Heart rate and oxygen saturation in our study were monitored in the morning (once-daily (control) group) or overnight (overnight (experimental) group). Our findings show that the mean heart rate in both groups increased significantly during the pre-phase compared with the mean of the stable and

post phase, despite day-to-day variation in the once-daily group not crossing the significance level. In the overnight group it crossed the significant level from day-to-day variation on several days and from day -5 for five consecutive days (Figure 27). The mean of heart rate in the once-daily group increased 7 beats min^{-1}, which is consistent with the reported increase of heart rate during exacerbation by other studies (115, 161). The maximum increase of heart rate in the overnight group was 10 beats min^{-1}. We noted that the variation of heart rate in the overnight group was smaller (±1.8) beats min^{-1}compared to the variation in the other group (±3.6) beats min^{-1}, which supports the hypothesis that overnight monitoring of heart rate might enhance the detection of exacerbations.

The use of oxygen saturation to predict COPD exacerbation has been previously examined. Hurst et al. reported that oxygen saturation from 13 exacerbations fell from baseline by a mean of 1.2% two days into the exacerbation (115). Other studies have reported that oxygen saturation fell 1-3 days prior the onset of exacerbation by 1-2% (110, 128, 161). In our study, the mean oxygen saturation in the once-daily group fell by 2% ($p > 0.050$) one day before the exacerbation. In contrast, the oxygen saturation of overnight group had fallen by 1.2% for several days before the onset of the exacerbation ($p=0.050$). Variation (SD) in the overnight group (±0.36) was less than the once-daily group (±0.81), which again might increase the potential to detect changes over time due to COPD exacerbation.

In a previous systematic review (chapter 3), we reported that the majority of studies were taking measurements intermittently and at different times with different frequencies (118). This approach might not be the best for using physiological variables to detect exacerbations as the signal might be affected by external factors as exercise and anxiety. In our study, we have shown that overnight monitoring of heart rate (which crossed the threshold at day -7) and oxygen saturation (which crossed the threshold at day -7) showed changes earlier than the once-daily (morning) monitoring, which again suggests that overnight monitoring might have eliminated non-COPD effects from the signal.

The correlation between symptoms and physiological measures at COPD exacerbation is still unclear. There are multiple ways to assess the 'severity' of change in a variable such as symptoms including peak change from baseline, duration of change above baseline, or an area-under-the-curve approach which is a composite of intensity and duration of change. Hence, we have applied different exploratory methods to assess the relationship between symptoms and physiological variables. All these methods did not show consistent findings.

Our data showed that changes in physiological variables are correlated with changes in symptoms (Table 13). We anticipated that variables would correlate with each other most closely in periods where patient become unwell. Aforementioned studies have shown that changes in physiological variables and symptoms started a few days before

exacerbation before returning to normal, which suggests that the most unwell period is the days just before and after the exacerbation presentation, as would be expected. Our findings showed that most of the variables were correlated in that period “one week pre- and post-exacerbation” for both groups, and for the overnight measurement group the “two weeks pre-exacerbation” period also had more variables correlated with each other. Peak expiratory flow was the variable that was correlated most closely with symptoms (Table 13 and Table 14) suggesting that peak expiratory flow for home monitoring in patients with COPD, but as described above the absolute changes in PEF are small and within the measurement error of the device.

In the context of using tele-health technology to monitor or predict COPD exacerbations, a multifaceted approach is needed to maximise the outcomes. In this study we used subjective and objective measures to allow earlier detection of exacerbations, and findings showed that detection of exacerbations could be aided by physiological variable (objective measures). Moreover, changes in symptoms were correlated with changes in physiological variables. Relying on only subjective measures may lead to either under or over diagnosis of exacerbations; therefore, the use of supportive objective measurements could increase the diagnostic certainty level. In the context of clinical trials, researchers could use this monitoring modality to increase the certainty about the frequency of changes in patient clinical state and avoid missed unreported exacerbations

Unexpectedly, our COPD exacerbations were dissimilar between the two groups and it is not clear how this may have affected the results. The concept of exacerbation heterogeneity is increasingly recognised but this has not previously been studied in relation to tele-health monitoring.

During the study period, a few phone calls were received from both groups enquiring about their measurements and daily readings. Participants generally were seeking advice on their current health-status, has implications for clinical practice if this was provided as a service. We believe that the number of calls could be high and decrease limitation of this work is that we did not systematically document the frequency, duration and outcomes of the calls that we received. Therefore, we suggest that future studies of tele-health in COPD should consider monitoring such communications.

The amount of data obtained from the overnight group was considerable (one measure of heart rate and oxygen saturation every four seconds, each night, every night), and these data have shown the potential of detecting exacerbation by assessing physiological parameters earlier than symptoms. This approach (overnight) and data could facilitate the development of a new algorithm that can be implemented in tele-health systems to predict/detect exacerbation earlier, if it could show better outcomes with more advanced mathematics. We attempted to use Machine learning approaches to explore other methods to analyse the data, but that proved impossible due to technical problems (mentioned below).

Strengths and Limitations

To our knowledge this is the first study that monitored COPD patients overnight until exacerbation. In this study, we managed to take the measures of each patient in the overnight group every four seconds which reduced the day-to-day variability in the measurement compared to the once-daily group. Physiological signal was changing prior to exacerbation earlier than symptoms. However, the equipment used on the overnight group was not designed for continuous monitoring for that period of time (six months); therefore, encountered a number of technical issues in this study with the wrist pulse-oximeter equipment: a) battery was supposed to be changed every week (within 30 seconds), which was a challenging task for the participants to achieve, b) as a result of the participants taking more than 30 seconds to change the battery, the date stamp and time was reset every week, which made the process of collecting the data challenging. No solution was found for this problem by the company and other software developers we contacted. Thus, data were downloaded manually (two weeks for the stable-phase, two weeks for the pre-exacerbation phase, and two weeks for the post-exacerbation phase), and matched with data provided by the participants on the diary card by hand. This took a considerable amount of time and a solution would need to be found to further progress this work, generating sufficient data for machine learning. The drop out rate in this study was higher than expected (58%). We believe this was generally due to: a) patients lost interest in the study, b) the duration of the study, as patients felt the protocol included too many things to do each day over such

a long period, and c) there was no real-time interaction with the healthcare provider with regard to their measurements. These should be specifically addressed in any future tele-health projects. In particular, we believe if we were able to manage to have real-time intervention with patients enrolled in tele-health projects this would increase the adherence/acceptance to the study. Although findings from this study have shown the potential of physiological variables to assist the detection of COPD exacerbation, we cannot draw a bold conclusion on efficacy due to the small number of exacerbations captured (27/44) as a consequence of the higher than expected drop-out rate. This means the study is under powered to show a true difference in time to treatment between changes in symptoms and changes in physiological variables.

6.4 Conclusion

Monitoring physiological variables combined with symptoms could facilitate the earlier detection of exacerbations. Overnight pulse-oximetry monitoring allowed earlier detection than once daily monitoring by reducing the SD of the measurement. Symptoms and physiology variables are correlated when a patient is unwell. Efforts to develop new monitoring equipment for the purposes of continuous monitoring are required.

If overnight monitoring was to be useful in clinical practice, it must be acceptable to patients and in the final experimental chapter I go on to explore the acceptability of overnight monitoring in these patients.

7 Patients' acceptance of overnight continuous pulse oximetry monitoring: an exploratory survey

7.1 Aim

To evaluate patients' acceptance of continuous overnight home pulse-oximetry monitoring.

The findings of this chapter will be included with the findings from chapter 7 and will be submitted to the 2019 ATS conference and written as one paper.

7.2 Method

Study design

A cross-sectional questionnaire study was conducted on COPD patients receiving overnight home pulse-oximetry monitoring as part of a research project based at the Royal Free Hospital in London (Appendix 10). The questionnaire consisted of 10 questions, which covered four main domains: a) willingness to use the monitoring equipment (two questions), b) effect on sleep quality (two questions), c) convenience of the device (four questions), and d) charging preference (one question). Patients' responses were recorded using a visual analog scale that ranged from 0-10, where the anchor statement at 0 means 'strongly disagree' and 10 means 'strongly agree'. Question number 10 asked the patients to write any free-text comment they had about the tool and its acceptability. As each question of the first nine questions was scored out of 10 points, the highest possible total score was 90 (the higher the score, the greater the acceptance). To achieve this, at the time of analysing the data, questions 3, 4, 6, 7, and 9 were scored reversely such that a score of 0 means strongly agree, and 10 means strongly disagree. Compliance was defined as a patient who was monitored

daily for three to six months or until they reported an exacerbation episode (whichever was sooner).

Method of sampling

A convenience sampling strategy was used in this study. Based on this, patients who met the inclusion criteria and who were willing to participate in the study were included.

Eligibility criteria

Inclusion criteria

- Patient diagnosed with COPD.
- Patients randomised to continuous overnight pulse-oximetry (using the Nonin wristOx2 1350) for overnight monitoring.
- Patients with accessible pulse-oximetry data.

Exclusion criteria

- Patient who used the device for one night only.

Study procedure

All patients recruited in the experimental arm of the domiciliary monitoring study were asked to complete this survey after they had completed, or just prior to being withdrawn from the study. This survey was self-administered by the patient at the time they returned the monitoring equipment.

Statistical analysis

The statistical package for social since software (SPSS) version 24 was used to analyse the data. Categorical data are presented as frequency (percentage), and continuous data are presented as mean ± standard deviation (SD). Continuous data with normal distribution are presented as mean ± standard deviation (SD). Total acceptability score is presented as mean (SD) as the data were normally distributed. Patients' acceptability scores were interpreted in three categories: 0-30 low acceptability, 31-60 moderate acceptability, and 61-90 high acceptability. Univariate and multivariate linear regression analyses were applied in order to identify patient characteristics associated with acceptability of use of the home pulse oximeter monitoring device. Two regression models were used, the first model included patients' demographics such as age, gender, and domestic situation. The second model included patients' demographics and other clinical measures of interest, such as FEV_1, MRC, and the Charlson Comorbidity Index.

7.3 Results

7.3.1 Patients characteristics

The questionnaire was distributed to 30 COPD patients who had used a continuous overnight wrist pulse oximeter for at least two days. A total of 29 participants completed the questionnaire, with a response rate of 97%. 72% of participants were compliant with being monitored daily for three to six months or until they reported an exacerbation episode (whichever was

sooner). The characteristics of patients who participated in the study are presented in Table 17. The mean (SD) age of the patients was 70.3 (±8.2) years. 55% of them were male (n=16), and the mean (SD) BMI was 27.7 (±6.5) kg/m^2. The majority of the patients were ex-smokers (79%). 59% of the patients reported that they were living alone.

The mean (SD) number of COPD exacerbations within the past 12 months was 2.1 (±1.4). The mean Charlson (SD) Comorbidity Index score was 4.0 (±1.1). The mean (SD) Medical Research Council breathlessness (MRC) score was 2.8 (±0.9), and the mean (SD) percentage of FEV_1 was 52.0% (±19.6). With regard to sleepiness scores (Epworth), and risk of obstructive sleep apneoa scores (STOP-Bang), the majority of patients were within normal range (93%) and intermediate risk (52%), respectively.

Table 17. Participated patients' (n=29) demographics and clinical measures.

Demographics	
Age mean (±SD)	70.3 (±8.2)
Gender (Male, No. %)	16 (55.2)
BMI mean (±SD)	27.7 (±6.5)
Smoking status No. (%)	
Ex-smoker	23 (79.3)
Current smoker	6 (20.0)
Do you live with someone (Yes: No. %)	12 (41.4)
Clinical measures	
Number of exacerbation mean (±SD)	2.1 (±1.6)
Charlson comorbidity index mean (±SD)	4.0 (±1.1)
STOP-Bang No. (%)	
Low-risk	7 (24.1)
Intermediate risk	15 (51.7)
High risk	7 (24.1)
FEV1% mean (±SD)	52.14 (±19.6)
MRC mean (±SD)	2.79 (±0.9)
Epworth No. (%)	
Normal range	27 (93.1)
Abnormal range	2 (6.9)

7.3.2 Acceptability of daily overnight pulse oximeter monitoring

The total average acceptability score for continuous overnight home pulse oximeter ranged between 34.1 to 82.4. Patients had an overall moderate acceptability score with a mean (SD) total score of 59.8 (±12.6). Patients' acceptability scores were then examined by the four main domains: a) willingness to use the monitoring tool, b) the effect on sleep quality, c) convenience of the tool, and d) charging preference. Patients' acceptability scores per sub-scale were not the same. Patients showed the highest acceptability score for willingness to use the monitoring tool with a mean (SD) score of 7.6 (±2.3). The lowest sub-scale score was for the charging preference with a mean (SD) score of 3.8 (±3.4). Further detail on patients' acceptability score per sub-scale is reported in Table 18.

Table 18. Patients' acceptability scores per sub-scale.

Questionnaire score	Mean score (SD)
Willingness to use the tool	7.6 (±2.3)
Effect on sleep quality	6.7 (±3.3)
Convenience of the tool	6.9 (±1.9)
Battery charging preference	3.8 (±3.4)

Patients' free-text comments on the acceptability of continuous overnight pulse oximetry monitoring could be grouped into the following themes describing their experience with the equipment: a) design, b) convenience during sleep, c) comfort, d) overall convenience, e) usefulness, and f) convenience in specific circumstances. Table 19 describes the themes from patient feedback. The majority of the patients (55%) did not report any comments. However, 14% of patients reported that the design of the

equipment was not convenient (in terms of screen font size being small and the wrist strap being too long, for example).

Table 19. Patients' themes and feedback on continuous pulse oximeter monitoring.

Themes of patients' feedback on the tool	No.	%
No comments	16	**55.2**
Design not convenient	4	**13.8**
Not convenient during sleep	3	**10.3**
Uncomfortable	2	**6.9**
Usefulness	2	**6.9**
Beneficial for the patient	1	**3.4**
Convenient during specific circumstances (e.g. exacerbation)	1	**3.4**

7.3.3 Predictors of home pulse oximeter acceptability level

The use of two multivariate regression models showed no statistically significant associations between patient demographics or their clinical measures and acceptability level (P>0.05). However, univariate linear regression showed that patients who had a higher Charlson Comorbidity Index score and who were living alone had higher acceptability (p= 0.013, p= 0.022) respectively (Table 20). There was no evidence of association between compliance and patient acceptability of continuous overnight pulse oximeter monitoring (p= 0.124).

Table 20. Univariate linear regression analyses of demographics and clinical predictors of interest.

Model	Standardised coefficients	P value
Epworth	0.139	0.473
MRC	0.081	0.678
FEV_1%	0.013	0.945
Stop-Bang	0.157	0.416
Comorbidity index	0.453	0.013*
Number of exacerbations	-0.042	0.827
Living alone	0.424	0.022*
Smoking status	-0.115	0.552
BMI	-0.063	0.747
Gender (male)	0.018	0.925
Age	0.249	0.192
Compliance	0.292	0.124

* $P < 0.05$

7.4 Discussion

This study aimed to evaluate patients' acceptance of continuous overnight home pulse-oximetry monitoring. Our study did not show any significant correlation between patient acceptance levels and patient compliance. We found that living alone and comorbidity were significantly associated with overall acceptance (in univariate analysis). The overall acceptance of the patients was moderate, with a mean (SD) score of 59.8 (±12.6). Willingness to use the monitoring tool had the highest sub-scale

score with a mean (SD) of 7.6 (±2.3), and battery-charging preference had the lowest sub-scale score with a mean (SD) of 3.8 (±3.4).

We found that patients with greater comorbidity (Charlson Comorbidity Index) were more accepting of being monitored daily with a home pulse oximeter. Patients diagnosed with more than one disease may be more eager to seek advanced management solutions related to improving their health status. With regard to the association between patients' living status and patient acceptance, we found that patients who were living alone had higher acceptability. We are not aware of any previous studies examining the effect of comorbidity, or living status on acceptance of tele-health in COPD patients.

A previous study by Ernst and Bergus showed a high satisfaction rate among 235 patients who underwent 24 hours of continuous monitoring, using Ambulatory Blood Pressure Monitoring (ABPM) technology (162). The researcher reported that 20% of patients were not comfortable with continuous monitoring. Meanwhile, in our study, only 7.0% were not comfortable, even though our follow-up was longer with a minimum of 48 hours and maximum follow-up of six months.

Patients in previous studies have shown a willingness to use home monitoring devices if they thought it would benefit their condition (163). This is consistent with our findings on the "willingness to use the tool" sub-scale which was the highest scoring compared to other sub-scales. This was

driven by a belief that continuous overnight monitoring would increase participants' awareness of their condition.

A number of studies did not show any significant relationship between patient variables such as age, gender, and BMI with the level of acceptance of monitoring (164). This was similar to our findings, except for the comorbidity score and patient living status (Table 20).

The identification of factors that could affect patient acceptance and tolerance of home monitoring, or tele-health, is important (165). In a study conducted on COPD patients using a tele-health system, the investigator reported that motivating patients during tele-health use and emphasising data relevancy are vital factors in tele-health enrolment rates (166). We have used a wrist pulse-oximeter in this study to monitor heart rate and oxygen saturation measures, which attracted the patients as pulse-oximetry is a common device to assess heart rate and oxygen saturation. We found that the patients became interested to evaluate their own daily measurements of heart rate and oxygenation, which we believe motivated them to use the device and accept the idea of monitoring. Another factor that should be considered is the required duration of use. This might affect patient levels of acceptance and tolerance. It should be noted that in a continuous monitoring study conducted by Ricci et al. to evaluate the acceptance of one-year continuous monitoring via a non-wearable device (164), they highlighted that the design of their tool had influenced the acceptance level of their patients. In our study, design-related questions were under the "convenience of the tool" sub-scale, which was rated as moderate to high on a visual analogue

scale with a mean (SD) of 6.9 (±1.9), despite the finger sensor and wrist strap not being comfortable.

Strength and Limitation

The strength of our survey is that, to our knowledge, this is the first study evaluating the acceptance rate of continuous overnight home pulse oximeter monitoring on COPD patients. There are several types of devices that can be used for home monitoring; the device used in this study was wearable, thus findings are limited to wearable pulse-oximeter devices only. In question 1 and 2, we acknowledge the potential of bias as the words used (‘perfect’, ‘painless’ and ‘convenient’) in both questions might have influenced the rating of participants by describing an overly-idealised situation. A further limitation is that all the patients included had consented before being monitored; therefore, they could already have had a reasonable acceptance of technology and monitoring.

7.5 Conclusion

There was good acceptance from COPD patients toward the use of home overnight monitoring devices. No correlation was observed between the level of acceptance and the level of compliance. The majority of patients were willing to be continuously monitored if they thought it would benefit them, including and particularly patients who were living alone and had more comorbidity – perhaps those who may benefit most. Patients preferred mains charged over battery devices.

8 Conclusion and suggested future studies

In this last chapter I have summarised the main findings of this PhD and included some suggestions for future work.

The key findings of this PhD could be summarised as:

1- Systematic review

- Previous studies examining the utility of physiological monitoring to predict exacerbations are small and heterogeneous, using different variables and different protocols.
- Heart rate and oxygen saturation were the most commonly measured variables (10/16 studies).

2- Clinical data

a) Tele-health data “Patient specific parameter thresholding to support domiciliary monitoring in COPD”:

- Setting a personalised alarm limit for oxygen saturation (but not heart rate) for each patient individually would result in a reduction in the number of alarms per day compared to alarm limits set using ‘standards’ – however, the ability to detect exacerbations may be affected.

b) Home non-invasive ventilation data:

- The method used to set the threshold (>1.96SD away from the stable mean) did not identify statistically significant changes in day-to-day variation prior to hospitalisation. NIV variables are not easy to measure outside the context of NIV.
- The mean difference between the three different phases (stable-phase, pre-phase, post-phase) was statistically significant in all variables except NIV usage/day.

3- National and international tele-health surveys:

- Around one third (16/52) of NHS community COPD services in England and Wales that responded to our survey are currently using tele-health. Globally, 45/138 (33%) of responded currently use tele-health – thus there is widespread use of tele-health in COPD (without an evidence base).
- The majority of responding healthcare providers thought tele-health was useful in COPD.
- Tele-health was most commonly delivered from a fixed monitoring station in England and Wales, whereas globally smartphones/tablet apps were the most common technology.
- The most common variables monitored via tele-health for COPD patients were oxygen saturation, heart rate, breathlessness and use of rescue medication.

- In England and Wales, alarm limits were most commonly personalised for each patient using various non-standardised techniques. Globally, patients' alarm limits were set using guidelines, which to the best of our knowledge do not exist.
- The majority of participants thought that a significant proportion of alarms received from tele-health systems were false.

4- Continuous Overnight Monitoring to Predict Exacerbations of COPD

- Symptom measures assessed using the CAT Score change significantly (>MCID) five days prior to patients receiving exacerbation treatment.
- Physiological parameters also change significantly before exacerbation onset, but changes in PEF are too small to be clinically useful.
- The time difference to receiving treatment between changes in symptoms and changes in physiology was not statistically significant.
- Overnight measurement of heart rate permitted earlier detection of exacerbation than once-daily measurement, because the SD of the variable when monitored overnight is smaller.
- Symptom severity was correlated with physiological parameters during the pre- and post-exacerbation phases.

5- Patients' acceptance of daily overnight monitoring

- There was moderate acceptance by COPD patients undergoing continuous overnight monitoring with a wearable pulse oximeter device.
- Living alone and higher comorbidity score (Charlson comorbidity index) were significantly associated with the patients' acceptance of continuous overnight monitoring via a wearable pulse oximeter, such that acceptance was highest in those who may have the greatest potential benefit.

Discussion

Based on the findings from this thesis we have identified gaps that need to be addressed about the use of tele-health in COPD. The number of patients diagnosed with COPD are increasing worldwide and therefore finding better solutions to their health needs, especially better prevention and treatment of exacerbations is required. Advances in technology could offer a solution to mitigate the burden of COPD, however, the existing literature did not show a solid evidence of efficacy due, in general, to the poor quality of current studies. Therefore, future studies should focus on conducting high-quality research studies on a large scale, developing novel techniques and assessing these against robust, clinically important outcome measures such as exacerbations and hospitalisation. They should consider using a standardised definition of exacerbation of COPD, and minimise the factors that could affect the generalisation of the outcomes, such as patient severity. If researchers could find a validated method to detect exacerbations earlier then this may contribute to lower the impact of exacerbations, help to improve the quality of life, and may lower the mortality and morbidity of the disease, which will then indirectly impact the economic effects of COPD.

Future work suggestions

1. We have shown that physiological variables might help in detecting exacerbations earlier, and measured variation using overnight monitoring of pulse-oximeter was much lower than once-daily monitoring; however, the device used in this study was not designed for this purpose. Therefore, in future work I will partner with a tech company to develop a wearable oximeter to measure heart rate, that transmits this data to a central server, and has automatic analysis to detect changes >2SD or detects “runs”. I will explore machine learning to these data to find the best pattern of changes in HR to detect an exacerbation. The development of new wearable oximeter should take in to consideration the size of the device, finger sensor shape, and the ability to transmit data in real-time.

2. Although symptoms are subjective, objective quantification of symptoms using a scale (such as the CAT questionnaire) could be used to provide earlier detection of exacerbation. The findings in this thesis showed that the CAT score changed prior to exacerbation. These tools are simple, safe and cheap to use compared to other techniques thus it might benefit healthcare systems with limited resources to implement, and therefore decrease the impact of COPD. A randomised controlled trial of CAT-guided exacerbation treatment could be conducted. In the experimental group, when CAT crosses the MCID above baseline, participants should start treatment. In the control group, participants should receive usual care. Primary outcome could be health-status using the St George Respiratory Questionnaire (SGRQ) at

one year. Secondary outcomes could include hospitalisation rate, number of courses of antibiotics used and lung function. All COPD patients susceptible to exacerbations could be included and then stratified based on the disease severity.

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Appendices

List of Appendices

Appendix 1

Table A1. Medline search strategy for the systematic review.

1	lung diseases, obstructive/ or exp. bronchitis/ or exp. pulmonary disease, chronic obstructive/	84,036	Advanced	Display Results More
2	emphysema$.mp.	31,994	Advanced	Display Results More
3	bronchiti$.mp.	30,780	Advanced	Display Results More
4	(obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.	96,121	Advanced	Display Results More
5	(copd or coad or cobd or aecb).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	33,479	Advanced	Display Results More
6	1 or 2 or 3 or 4 or 5	153,864	Advanced	Display Results More
7	telemedicine/ or telerehabilitation/	14,118	Advanced	Display Results More
8	(telemonitor* or tele-monitor* or tele-health* or telehealth* or telemedicine or tele-medicine or tele-rehabilitat* or telerehabilitat*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	18,772	Advanced	Display Results More
9	(e-health or ehealth or m-health or mhealth or mobile health).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	8219	Advanced	Display Results More
10	exp. Telemetry/	10,614	Advanced	Display Results More
11	(telemetr* or tele-metr*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	12,888	Advanced	Display Results More
12	Monitoring, Ambulatory/	6635	Advanced	Display Results More
13	(monitoring adj4 (ambulatory or home$)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	23,156	Advanced	Display Results More
14	Domiciliary.mp.	2364	Advanced	Display Results More
15	software/ or mobile applications/ or user-computer interface/	114,192	Advanced	Display Results More
16	(software* or app? or iphone or ipad or android or smartphone* or smart-phone*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary	205,344	Advanced	Display Results More

	concept word, rare disease supplementary concept word, unique identifier]			
17	or/7–16	284,600	Advanced	Display Results More
18	(exacerbat* or deteriorat*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	176,862	Advanced	Display Results More
19	heart rate/	149,127	Advanced	Display Results More
20	Pulse/	16,765	Advanced	Display Results More
21	((heart* or pulse* or cardiac) adj3 rate*).mp.	229,964	Advanced	Display Results More
22	respiratory rate/ or Respiration/	75,932	Advanced	Display Results More
23	((respirat* or breath*) adj3 rate*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	24,774	Advanced	Display Results More
24	exp. Oximetry/	13,116	Advanced	Display Results More
25	oximetr*.mp.	15,161	Advanced	Display Results More
26	Oxygen/	150,124	Advanced	Display Results More
27	SPO_2.mp.	3207	Advanced	Display Results More
28	oxygen.mp.	519,842	Advanced	Display Results More
29	(physiological adj4 (variable* or measure*)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	10,547	Advanced	Display Results More
30	early diagnosis/	19,913	Advanced	Display Results More
31	(early adj4 (detect* or diagnos*)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	176,122	Advanced	Display Results More
32	predict*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1,238,846	Advanced	Display Results More
33	or/18–32	2,291,354	Advanced	Display Results More
34	6 and 17 and 33	795	Advanced	

Table A2. Database keyword search strategy for the five databases.

Database	Subject Heading	Keyword
Medline	lung diseases, obstructive/ or exp. bronchitis/ or exp. pulmonary disease, chronic obstructive/ telemedicine/ or telerehabilitation/ exp. Telemetry/ Monitoring, Ambulatory/ software/ or mobile applications/ or user-computer interface/ heart rate/ Pulse/ respiratory rate/ or Respiration/ exp. Oximetry/ Oxygen/ early diagnosis/	emphysema$. bronchiti$. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)). (copd or coad or cobd or aecb) (telemonitor* or tele-monitor* or tele-health* or telehealth* or telemedicine or tele-medicine or tele-rehabilitat* or telerehabilitat*) (telemetr* or tele-metr*) (monitoring adj4 (ambulatory or home$)). Domiciliary. (software* or app? or iphone or ipad or android or smartphone* or smart-phone*). (exacerbat* or deteriorat*). ((heart* or pulse* or cardiac) adj3 rate*). ((respirat* or breath*) adj3 rate*). oximetr*. SPO_2. oxygen. (physiological adj4 (variable* or measure*)). (early adj4 (detect* or diagnos*)). predict*.
Embase	lung diseases, obstructive/ or exp. bronchitis/ or exp. pulmonary disease, chronic obstructive/ exp. telemonitoring/ or exp. telemedicine/ telerehabilitation/ exp. telephone telemetry/ or exp. telemetry/ exp. ambulatory monitoring/ computer program/ or exp. communication	emphysema$. bronchiti$. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)). (copd or coad or cobd or aecb). (telemonitor* or tele-health* or telehealth* or telemedicine or tele-medicine or tele-

	software/ or exp. mobile application/ exp. computer interface/ heart rate variability/ or exp. heart rate/ exp. pulse rate/ or exp. “heart rate and rhythm”/ exp. breathing/ or exp. breathing rate/ exp. oximetry/ or exp. measurement/ or exp. pulse oximetry/ exp. oxygen breathing/ exp. early diagnosis/	monitor*). (e-health or ehealth or m-health or mhealth or mobile health). (telemetr* or tele-metr*). ((respirat* or breath*) adj3 rate*). oximetr*. SPO_2. Oxygen (physiological adj4 (variable* or measure*)). (early adj4 (detect* or diagnos*)). predict*. (monitoring adj4 (ambulatory or home$)). Domiciliary. (software* or app? or iphone or ipad or android or smartphone* or smart-phone*). (exacerbat* or deteriorat*). ((heart* or pulse* or cardiac) adj3 rate*).
AMED	pulmonary disease chronic obstructive/ or bronchitis/ or pulmonary emphysema/ or lung diseases obstructive/ telemedicine/ home care services/ internet/ or exp. computers/ or software/ disease progression/ heart rate/ Pulse/ exp. Respiration/ Oxygen/ monitoring physiologic/ or respiratory function tests/ diagnosis/	emphysema$. bronchiti$. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)). (copd or coad or cobd or aecb). (telemonitor* or tele-monitor* or tele-health* or telehealth* or telemedicine or tele-medicine or tele-rehabilitat* or telerehabilitat*). (e-health or ehealth or m-health or mhealth or mobile health). (telemetr* or tele-metr*). ((monitoring adj4 (ambulatory or home$)). Domiciliary. (software* or app? or iphone or ipad or

		android or smartphone* or smart-phone*). (exacerbat* or deteriorat*). ((heart* or pulse* or cardiac) adj3 rate*). ((respirat* or breath*) adj3 rate*). oximetr*. SPO_2. oxygen. (physiological adj4 (variable* or measure*)). (early adj4 (detect* or diagnos*)). predict*.
CINAHL	(MH “Lung Diseases, Obstructive”) OR (MH “Bronchitis+”) OR (MH “Emphysema”) OR (MH “Pulmonary Disease, Chronic Obstructive+”) (MH “Telenursing”) OR (MH “Telepathology”) OR (MH “Remote Consultation”) OR (MH “Telemedicine”) OR (MH “Telehealth”) (MH “Telemetry”) (MH “Ambulatory Care”) (MH “Software”) OR (MH “Communications Software+”) OR (MH “Mobile Applications”) OR (MH “User-Computer Interface+”) (MH “Pulse”) OR (MH “Heart Rate”) (MH “Wireless Communications”) OR (MH “Telephone+”) OR (MH “Instant Messaging”) (MH “Respiratory Rate”) OR (MH “Respiratory Sounds”) (MH “Respiration+”) (MH “Oximetry+”) (MH “Oximeters+”) (MH “Oxygen”) (MH “Oxygenation”) OR (MH “Oxygen Saturation”) (MH “Monitoring, Physiologic”)	TX emphysema* TX bronchiti* TX (copd or coad or cobd or aecb) TX (obstruct* n3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) TX (telemonitor* or tele-monitor* or tele-health* or telehealth* or telemedicine or tele-medicine or tele-rehabilitat* or telerehabilitat*) TX (e-health or ehealth or m-health or mhealth or “mobile health”) TX (telemetr* or tele-metr*) TX monitoring n4 (ambulatory or home*) TX Domiciliary TX (app# or iphone or ipad or android or smartphone* or smart-phone*) OR TI software* OR AB software* TX (exacerbat* or deteriorat*) TX ((heart* or pulse* or cardiac) n3 rate*) TX (respirat* or breath*) n3 rate* TX oximetr* TX SPO_2

	(MH “Early Diagnosis”)	TX oxygen TX (physiological n4 (variable* or measure*)) TX (early n4 (detect* or diagnos*)) TX predict*
Cochran	[mh “lung diseases, obstructive”] [mh bronchitis] [mh “pulmonary disease, chronic obstructive”] [mh telemedicine] [mh telerehabilitation] [mh Telemetry] [mh “Monitoring, Ambulatory”] [mh software] [mh “mobile applications”] [mh “user-computer interface”] [mh “heart rate”] [mh pulse] [mh “respiratory rate”] [mh Respiration] [mh Oximetry] [mh Oxygen] [mh “early diagnosis”]	COPD emphysema* bronchiti* (obstruct* near/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) (copd or coad or cobd or aecb) (telemonitor* or tele-monitor* or tele-health* or telehealth* or telemedicine or tele-medicine or tele-rehabilitat* or telerehabilitat*) (e-health or ehealth or m-health or mhealth or mobile health) (telemetr* or tele-metr*) (monitoring near/4 (ambulatory or home*)) Domiciliary (software* or app or apps or iphone or ipad or android or smartphone* or smart-phone*) (exacerbat* or deteriorat*) ((heart* or pulse* or cardiac) near/3 rate*) ((respirat* or breath*) near/3 rate*) oximetr* SPO_2 Oxygen (physiological near/4 (variable* or measure*)) (early near/4 (detect* or diagnos*)) predict*

Table A3. Excluded studies in the systematic review.

First Author	Study Title	Reason
Malliopoulos, C., 2008	Continuous mobile services for healthcare: The health wear project	Article not available and no response from the author
Antoniades, N.C., 2012	Pilot study of remote telemonitoring in COPD	No physiological data shown and it does not address the prediction of COPD exacerbation
Jensen, M.H., 2012	Clinical impact of home telemonitoring on patients with chronic obstructive pulmonary disease	Not relevant (evaluated the impact of tele-health on patients, not in predicting exacerbation)
Jakobsen, A.S., 2013	Hospital-admitted COPD patients treated at home using telemedicine technology in The Virtual Hospital Trial: methods of a randomized effectiveness trial	Recruited non-stable COPD patients for preventing readmission
Jehn, M., 2013	Tele-monitoring reduces exacerbation of COPD in the context of climate change-a randomized controlled trial	Looked at the association between the weather and exacerbation.
Pinnock, H., 2013	Effectiveness of telemonitoring integrated into existing clinical services on hospital admission for exacerbation of chronic obstructive pulmonary disease: researcher blind, multicentre, randomised controlled trial	No physiological variation reported and not for predicting exacerbation
San Miguel, K., 2013	Telehealth remote monitoring for community-dwelling older adults with chronic obstructive pulmonary disease	No physiological variation reported and not for predicting exacerbation
Schou, Lone, 2013	A randomised trial of telemedicine-based treatment versus conventional hospitalisation in patients with severe COPD and exacerbation—Effect on self-reported outcome	Not for predicting exacerbation and recruited non-stable COPD patients
van der Heijden, M., 2013	An autonomous mobile system for the management of COPD	Designing a mobile system
Zhang, J., 2013	MIOTIC study: A prospective, multicenter, randomized study to evaluate the long-term efficacy of mobile phone-based internet of things in the management of patients with stable COPD	No physiological variation reported and not for predicting exacerbation
Ding, H., 2014	A pilot study of a mobile-phone-based home monitoring system to assist in, remote interventions in cases of acute exacerbation of COPD	Did not report any monitored physiological data
Ko, F.W.S., 2014	COPD care programme can reduce readmissions and in-patient bed days	Recruited non-stable COPD patients
Minami S., 2014	Ambulatory pulse oximetry monitoring in Japanese COPD outpatients not receiving	Monitored the patient's SPO_2%

	oxygen therapy	for a 24 h period only.
Jakobsen, A.S., 2015	Home-Based Telehealth Hospitalization for Exacerbation of Chronic Obstructive Pulmonary Disease: Findings from “The Virtual Hospital” Trial	Recruited non-stable COPD patients
Ringbaek, T., 2015	Effect of telehealthcare on exacerbations and hospital admissions in COPD: A randomised controlled trial	No physiological variation reported and not for predicting exacerbation

Appendix 2. A copy of the national survey presented in chapter 5.

Thank you for agreeing to take part in this survey. The aim is to explore the use of tele-health services in COPD patients across the UK, and examine which techniques healthcare providers use to set alarm limits. We define tele-health as home monitoring of symptoms, vital signs or other parameters with transmission of data back to the health-care facility. This survey will only take 5 minutes to complete.
All completed questionnaires will be entered into a draw to win a £50 Marks and Spencers voucher!

1. Which Trust do you work for?

2. Your role:

3. Is tele-health used by your Trust to monitor patients with COPD at home?

- ○ Yes
- ○ No

4. If yes, is tele-health (home monitoring) used for... (check all that apply).

- ☐ Baseline monitoring (to observe, advise or coach the patient in daily COPD care).
- ☐ To provide early detection of exacerbations
- ☐ To help monitor recovery from exacerbations
- ☐ Other (please specify)

1

5. The next question is about hardware in the home. What type of tele-health equipment do you use? (check all that apply)

- [ ] Smartphone/tablet App
- [ ] Monitoring station
- [ ] Fixed telephone
- [ ] Video phone
- [ ] Other (please specify)

6. On a scale 1 (not at all) to 10 (very much so), do you think tele-health is useful in COPD?

1 (not at all) 10 (very much so)

7. If you think tele-health is useful, what is it most useful for?

8. Which variable do you monitor, and if you set an automatic alarm for this variable how do you choose the alarm limits? (select all that apply).

	Do you monitor this?	How do you set the alarm limits?
Heart rate		
Oxygen saturation		
Respiratory rate		
Blood pressure		
Temperature		
Peak flow		
Hours of CPAP use		
Hours of NIV use		
Step Count		
Physical Activity		
Metabolic Equivalent data, e.g. from a treadmill		
Sleep quality		
Phlegm symptoms		
Cough symptoms		
Breathlessness symptoms		
Wheeze symptoms		
Use of rescue medication		

Other (Please specify)

3

9. If any alarm limits were personalised to a specific patient, how do you do that?

10. Do you think your method for personalising alarm limits is sensitive enough to identify an exacerbation?

- Yes
- No

11. If you personalise any alarms, on a scale 1 (not at all) to 10 (very much so), does personalising alarms makes the service more efficient than using arbitrary alarm limits.

1 (not at all) 10 (very much so)

12. Based on your experience of tele-health, approximately what percentage of alarms are false alarms? Your best guess is fine!

- 0-20%
- 20-40%
- 40-60%
- 60-80%
- 80-100%

13. How did you hear about this survey?

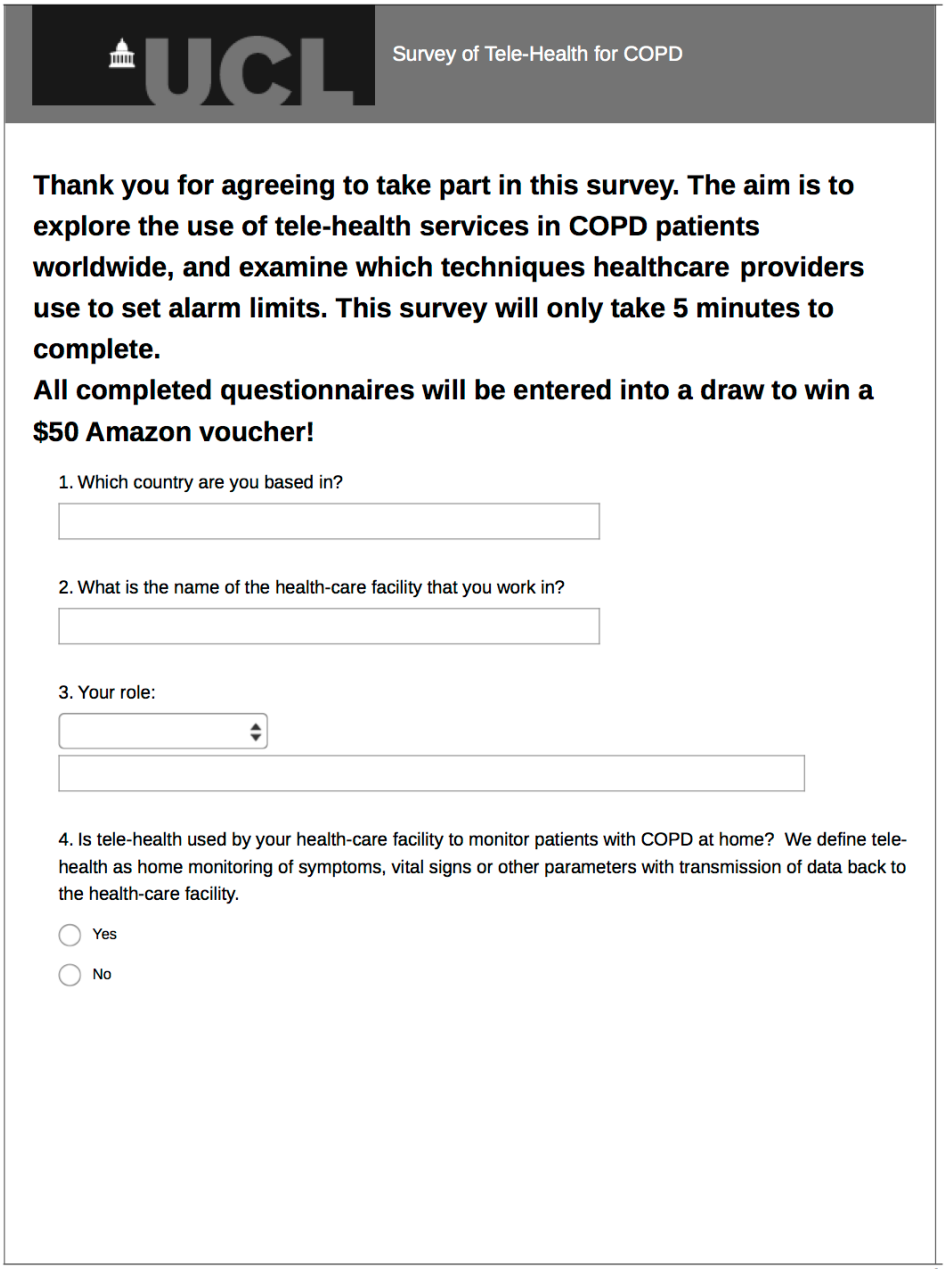
14. Please include your name and email if you wish to be entered into the draw for the voucher!

That's it, thank you, DON'T FORGET TO PRESS "DONE" below.

Name

Email Address

Appendix 3. A copy of the international survey presented in chapter 5.



UCL

Survey of Tele-Health for COPD

Thank you for agreeing to take part in this survey. The aim is to explore the use of tele-health services in COPD patients worldwide, and examine which techniques healthcare providers use to set alarm limits. This survey will only take 5 minutes to complete.

All completed questionnaires will be entered into a draw to win a $50 Amazon voucher!

1. Which country are you based in?

2. What is the name of the health-care facility that you work in?

3. Your role:

4. Is tele-health used by your health-care facility to monitor patients with COPD at home? We define tele-health as home monitoring of symptoms, vital signs or other parameters with transmission of data back to the health-care facility.

- Yes
- No

1

5. If yes, is tele-health (home monitoring) used for... (check all that apply).

- [ ] Baseline monitoring (to observe, advise or coach the patient in daily COPD care)
- [ ] To provide early detection of exacerbations
- [ ] To help monitor recovery from exacerbations
- [ ] Other (please specify)

6. The next question is about hardware in the home. What type of tele-health equipment do you use? (check all that apply)

- [ ] Smartphone/tablet App
- [ ] Monitoring station
- [ ] Fixed telephone
- [ ] Video phone
- [ ] Other (please specify)

7. On a scale 1 (not at all) to 10 (very much so), do you think tele-health is useful in COPD?

1 (not at all) 10 (very much so)

8. If you think tele-health is useful, what is it most useful for?

9. Which variable do you monitor, and if you set an automatic alarm for this variable how do you choose the alarm limits? (select all that apply).

	Do you monitor this?	How do you set the alarm limits?
Heart rate		
Oxygen saturation		
Respiratory rate		
Blood pressure		
Temperature		
Peak flow		
Hours of CPAP use		
Hours of NIV use		
Step Count		
Physical Activity		
Metabolic Equivalent data, e.g. from a treadmill		
Sleep quality		
Phlegm symptoms		
Cough symptoms		
Breathlessness symptoms		
Wheeze symptoms		
Use of rescue medication		

Other (Please specify)

3

10. If any alarm limits were personalised to a specific patient, how do you do that?

11. Do you think your method for personalising alarm limits is sensitive enough to identify an exacerbation?

- Yes
- No

12. If you personalise any alarms, on a scale 1 (not at all) to 10 (very much so), does personalising alarms makes the service more efficient than using arbitrary alarm limits.

1 (not at all) 10 (very much so)

13. Based on your experience of tele-health, approximately what percentage of alarms are false alarms? Your best guess is fine!

- 0-20%
- 20-40%
- 40-60%
- 60-80%
- 80-100%

14. How did you hear about this survey?

15. Please include your name and email if you wish to be entered into the draw for the voucher!

That's it, thank you, DON'T FORGET TO PRESS "DONE" below.

Name

Email Address

Appendix 4. Epworth Sleepiness Scale.

Royal Free London NHS
NHS Foundation Trust

Epworth Sleepiness Scale

Name Participant's study code: Date:

age: sex:

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

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

0 = would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

Situation	Chance of dozing
1- Sitting and reading	
2- Watching TV	
3- Sitting, inactive in a public place (e.g. a theatre or a meeting)	
4- As a passenger in a car for an hour without a break	

1

5- Lying down to rest in the afternoon when circumstances permit . . . . . ☐

6- Sitting and talking to someone . . . . . ☐

7- Sitting quietly after a lunch without alcohol . . . . . ☐

8- In a car, while stopped for a few minutes in the traffic . . . . . ☐

Total . . . . . ☐

Score:

0-10 Normal range

10-12 Borderline

12-24 Abnormal

Appendix 5. Stop-Bang Questionnaire.

Royal Free London NHS
NHS Foundation Trust

Stop BANG Questionnaire

Participant's study code: Age:
Height: Weight:
Date:

	Please circle
Snoring? Do you Snore Loudly (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night)?	**Yes/No**
Tired? Do you often feel Tired, Fatigued, or Sleepy during the daytime (tired enough that you could fall asleep while driving)?	**Yes/No**
Observed? Has anyone Observed you Stop Breathing or Choking/Gasping during your sleep?	**Yes/No**
Pressure? Do you have or are you being treated for High Blood Pressure?	**Yes/No**
Body Mass Index more than 35 kg/m2?	**Yes/No**
Age older than 50 years old?	**Yes/No**
Neck size: Is it large? (Measured around Adams apple) For male, is your shirt collar 17 inches/43 cm or larger? For female, is your shirt collar 16 inches/41 cm or larger?	**Yes/No**
Gender: Male?	**Yes/No**

1

Appendix 6. Patient information sheet.

Royal Free London NHS
NHS Foundation Trust

Royal Free Hospital
Pond Street
London NW3 2QG
Switchboard: 020 7794 0500
www.royalfree.nhs.uk

Domiciliary Monitoring to Predict Exacerbations of Chronic Obstructive Pulmonary Disease

Version: 2.0 **Date: 22 March 2016**

IRAS Project ID: 201527

You are being invited to take part in a research study. Please take the time to read the following information carefully and discuss it with others. Ask us if there is anything that you do not understand or if you would like more information.

What is The Study About? Why is it Being Done?

People living with COPD are prone to chest infections called 'exacerbations'. The earlier treatment is started the better, but it can be difficult to distinguish exacerbations from day to day symptoms changes. Our research is designed to address this. We will collect information about COPD symptoms, heart rate, and oxygen saturation that may allow us to detect COPD exacerbations at an earlier stage. No treatment will be given specifically as part of this study.

What Happens In The Study?

You will have an initial lung assessments at the beginning of the study (first visit), and then be randomly allocated in one of our two groups. One group will have overnight monitoring of heart rate and oxygen levels, the other group will take this measurement just once each day, in the morning. If you are allocated to the overnight group, we may also monitor your overnight activity using a sensor worn on the arm. Three in-person visits will be scheduled for you. Study visits will be carried out at the Royal Free Hospital.

Why Have I Been Chosen?

You have been asked to join this study because you have COPD. You will already have had investigations for this.

What Does The Study Involve?

In the first visit before you start the study, you will have a detailed lung assessment by the researcher, including questionnaires and breathing tests that may be familiar to you. Two groups will be involved in this study, and you will be assigned to one of the groups randomly. Group 1,

Royal Free Hospital
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will be asked to complete a short eight question questionnaire, diary card, measure the peak flow, oxygen saturation, and heart rate every morning. This should take not more than a few minutes each morning Group 2, will be asked to wear a pulse oximeter on the wrist (it looks a little like a standard wrist watch) to record their heart rate and oxygen saturation during sleep, plus answer the questionnaire, diary card, and measure the peak flow in the morning. We will ask some patients in this group to wear an overnight activity sensor on the arm, in some people for just two weeks but in others every day for six months. We will explain which one applies to you before you decide whether to take part. One week after the first visit we will contact you to make sure that you are getting on okay with the equipment. One week later (two weeks after the start of the study) we will arrange an appointment to download the first data from the sensor and, if you had an activity monitor, to collect that. In-person visits will then be scheduled for you three and six months after the start of the study, unless you experienced a chest infection (exacerbation). If you experience an exacerbation we ask you to call us and once you are better we will collect the study equipment. If you do not have an exacerbation we will collect the equipment at the six month visit.

What Are The Possible Risks of Taking Part?

This is an observational study (we are not changing treatment) and does not include anything other than monitoring. Therefore, we don't anticipate any harm or risk. As no drugs are prescribed as part of this study, the only potential risks are those associated with the initial breathing tests, which are minimal (routine spirometry test).

Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.
All information collected about you during this study will be confidential. Your information will be stored with a study code and number. Your name will not be used in the study at all. The activity data may be shared with colleagues in Industry, who are supplying this equipment. No personally identifiable data will be shared at all.

Participation

It is up to you and your family to decide whether you want to be part of this study. If you do not want to be in this study, that is okay and your usual NHS care will continue as normal. You can stop during the study at any time without giving a reason. Your doctor will still look after you as normal. We hope, though, that you will tell us why you wish to stop the study.

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What if there is a problem" or "What happens if something goes wrong?

If you are concerned about any aspect of this study, please speak to the researchers who will do their best to answer your questions. Please contact: 020 7794 0500 Extension 34301. If you remain unhappy, you can make a formal complaint through the National Health Service (NHS) complaints procedure. Details can be obtained through the University College London Hospitals (UCLH) Patient Advice and Liaison Service (PALS) on 0207 3447 3041, email: PALS@uclh.nhs.uk, address: PALS, Ground Floor Atrium, University College Hospital, 235 Euston Road, London, NW1 2BU. University College London (UCL) holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Thank you for taking time to consider this study. Please ask any questions and let us know if there are things that you do not understand, or would like more information about.

Please address any further questions to:

Dr. John Hurst, Respiratory Consultant, Royal Free Hospital.

Mr. Ahmed Alrajeh, PhD student at University College London.
Tel: 020 7794 0500 extension 34301.
Mobile: 074 9251 2028
Ahmed.rajeh.15@ucl.ac.uk

Thank you for taking the time to read this information sheet.

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Appendix 7. Consent form.

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Royal Free Hospital

Study Number:

Participant Identification:

Researcher name: Ahmed Al Rajeh

IRAS Project ID: 201527

CONSENT FORM

Domiciliary Monitoring to Predict Exacerbations of COPD

	Please initial box
1. I confirm that I have read the information sheet dated **22 March 2016 (version 2.0)** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the respiratory research team from Royal Free Hospital, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐

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4. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. ☐

5. I understand that the information held and maintained by the respiratory research team (chief investigator, researcher, and research assistance) from Royal Free Hospital and other central UK NHS bodies may be used to help contact me or provide information about my health status. ☐

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

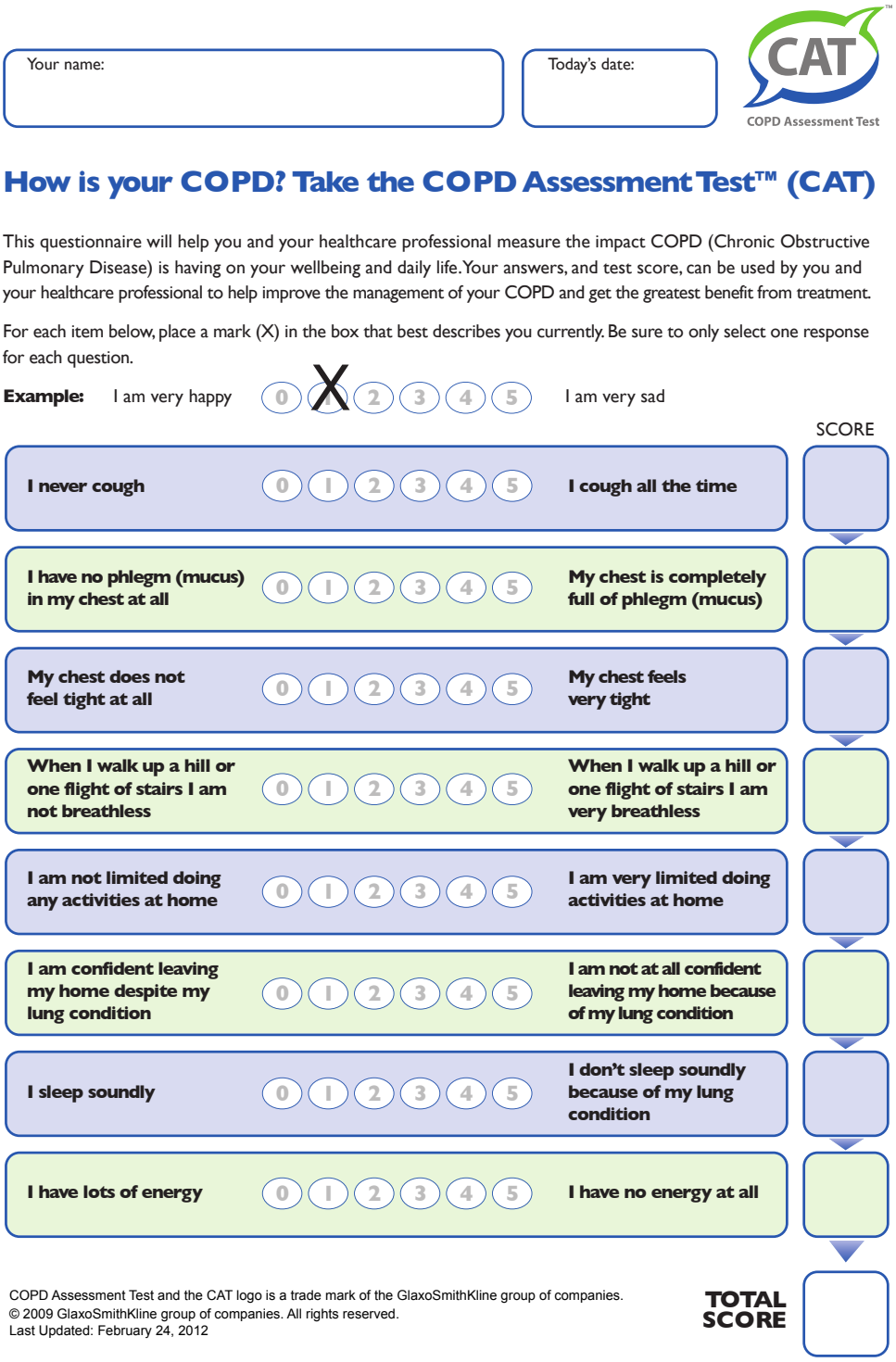
Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

Appendix 8. Medical Research Council.

MRC Dyspnoea Scale	
1	Breathless only with strenuous exercise
2	Short of breath when hurrying on the level or up a slight hill.
3	Slower than most people of the same age on a level surface or Have to stop when walking at my own pace on the level.
4	Stop for breath walking 100 meters or After a walking few minutes at my own pace on the level
5	Too breathless to leave the house.

Appendix 9. COPD Assessment Test (CAT).



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	

Appendix 10. Participants' acceptance survey.

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Participant's Acceptance Survey

This questionnaire will help us to measure your acceptance of continuous home pulse oximetry monitoring. Your answers will help us to improve the care we provide for COPD patients in the future. Kindly place a mark (E.g. X) anywhere on the line below each question to indicate your opinion.

For example:

X

Strongly disagree Strongly agree

1. If a perfect, painless, convenient sensor could predict when I was going to get a chest infection, I would be willing to use it every night.

Strongly disagree Strongly agree

2. If perfect, painless, convenient sensor could predict when I was going to get a chest infection, I would be willing to use it all the time (day and night).

Strongly disagree Strongly agree

3. The device I was wearing disturbed my sleep.

Strongly disagree Strongly agree

4. The device I was wearing increased the amount of time it took me to fall asleep.

Strongly disagree Strongly agree

5. It was easy to fix the device to my wrist.

Strongly disagree Strongly agree

1

6. The finger probe tended to fall off whilst I was asleep.

Strongly disagree Strongly agree

7. The device I was given is too big.

Strongly disagree Strongly agree

8. The readings on the screen are clear.

Strongly disagree Strongly agree

9. Charging the device with an electric charger would be more convenient than changing the battery.

Strongly disagree Strongly agree

10. Any additional comments?

Thank you for taking the time to complete this questionnaire.

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Publications

Appendix 8. Systematic review

Journal of
Clinical Medicine

MDPI

Article

Monitoring of Physiological Parameters to Predict Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): A Systematic Review

Ahmed M. Al Rajeh * and John R. Hurst

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Abstract: Introduction: The value of monitoring physiological parameters to predict chronic obstructive pulmonary disease (COPD) exacerbations is controversial. A few studies have suggested benefit from domiciliary monitoring of vital signs, and/or lung function but there is no existing systematic review. Objectives: To conduct a systematic review of the effectiveness of monitoring physiological parameters to predict COPD exacerbation. Methods: An electronic systematic search compliant with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted. The search was updated to April 6, 2016. Five databases were examined: Medical Literature Analysis and Retrieval System Online, or MEDLARS Online (Medline), Excerpta Medica dataBASE (Embase), Allied and Complementary Medicine Database (AMED), Cumulative Index of Nursing and Allied Health Literature (CINAHL) and the Cochrane clinical trials database. Results: Sixteen articles met the pre-specified inclusion criteria. Fifteen of these articules reported positive results in predicting COPD exacerbation via monitoring of physiological parameters. Nine studies showed a reduction in peripheral oxygen saturation (SpO_2%) prior to exacerbation onset. Three studies for peak flow, and two studies for respiratory rate reported a significant variation prior to or at exacerbation onset. A particular challenge is accounting for baseline heterogeneity in parameters between patients. Conclusion: There is currently insufficient information on how physiological parameters vary prior to exacerbation to support routine domiciliary monitoring for the prediction of exacerbations in COPD. However, the method remains promising.

Keywords: COPD; exacerbation; physiological signs; vital signs; lung function; home monitoring; telehealth

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a serious health matter, which significantly impacts the individual's quality of life. According to the World Health Organisation, in 2004, 65 million people were diagnosed with COPD globally [1]. In 2012, three million people died because of COPD [2], and thus COPD is anticipated to be the third leading cause of death by 2020 if no action is taken [3]. COPD, even when optimally managed, is associated with periodic deteriorations in respiratory health called exacerbations. Exacerbations are defined in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) document *"as an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication"* [4]. Exacerbations can lead to decline in the patient's overall function, causing hospitalisation, and/or death. Therefore, health care facilities, societies, and individuals have a common interest in better understanding how to prevent and manage exacerbations, reduce disease progression, and support patient self-management. To achieve this, early detection of exacerbations and prompt access to therapy and health services are

needed. Detecting COPD exacerbation earlier will allow prompt initiation of treatment [4]; therefore facilitating faster recovery and outcomes. This may result in a reduced number of hospital admissions, and as well as a reduction in healthcare consumption.

It is recognised that whilst defined by changes in symptoms, exacerbations are also associated with alterations in physiological variables. In 2010, Hurst et al. [5] examined the ability of domiciliary pulse oximetry and peak flow to distinguish exacerbations from day to day fluctuations. They reported that changes in heart rate, peripheral oxygen saturation (SpO_2%), and peak flow were significantly different just before and during an exacerbation. Rapid advancement in technology has offered numerous solutions targeting the management of chronic diseases (collectively known as tele-health). Tele-health is a form of distance communication between the patient and the healthcare provider for monitoring, communicating, managing or facilitating intervention [6]. Tele-health may monitor symptoms, and/or physiology parameters. Tele-health has shown some success in chronic disease management. The PROMETE study conducted in 2014 in Spain by Segrelles et al. reported a reduction in acute noninvasive ventilation (NIV) usage ($p < 0.0001$), emergency department (ER) visits ($p = 0.001$), admissions ($p = 0.015$) and bed days ($p = 0.018$) [7]. More recent studies in COPD have not been positive [8], perhaps reflecting the heterogeneity of COPD.

The objective of this systematic review was to summarise and report the value of domiciliary physiological monitoring in predicting exacerbations in patients with COPD.

2. Methods

2.1. Search Strategy

This systematic review (PROSPERO registration CRD42016046643) is compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards [9]. The search was completed up to April 6, 2016. The search was performed in Medical Literature Analysis and Retrieval System Online, or MEDLARS Online (Medline), Excerpta Medica dataBASE (Embase), Allied and Complementary Medicine Database (AMED), Cumulative Index of Nursing and Allied Health Literature (CINAHL), and the **Cochrane** clinical trials database. The search terms used are detailed in the Appendix A, Tables A1 and A2. In addition to the electronic database search, the reference list of eligible articles was also screened.

2.2. Inclusion Criteria

The studies included in this review met the following criteria: (1) Stable COPD; (2) Domiciliary monitoring; (3) Monitoring any physiological variables; (4) Reporting statistical analysis of the measured physiological variables; (5) Prediction of exacerbations via physiological variables.

2.3. Exclusion Criteria

We excluded the following: (1) Books; (2) Systematic reviews; (3) Non-English manuscripts; (4) Conference abstracts with no full-text; (5) Non-full text articles.

The main outcome of interest was variation in physiological parameters before and during COPD exacerbations, and the ability of measuring changes in physiological variables to provide early detection of COPD exacerbations.

2.4. Data Collection

Screening of the titles and abstracts was performed by the first author to eliminate all non-relevant studies. Titles and abstracts potentially relevant were read in full-text to evaluate if they were eligible or not. In addition to screening and evaluating for eligibility, the reference list of the eligible articles was screened. The second author confirmed the eligibility. Disagreement on five studies between authors was resolved after discussion.

2.5. Quality Assessment

The quality assessment was performed by each author individually based on two different modified scales, the Cochrane tool [10] and Newcastle-Ottawa scale [11]. The Cochrane quality assessment tool consists of seven questions to evaluate randomised studies included in this review. The Newcastle-Ottawa scale consists of seven questions used to assess cohort and non-randomised studies included in this review. The assessment was performed by each author individually and any disagreement was solved by discussion.

2.6. Synthesis of Results

The primary purpose of this systematic review was to assess the feasibility of predicting COPD exacerbations by domiciliary monitoring of physiological parameters. Because of significant methodological heterogeneity between included studies, meta-analysis was not conducted. However, a narrative synthesis of the results of the studies was performed and full details of the included studies are reported in Tables 1 and 2.

Table 1. Detailed description of the 16 included studies.

Author	Subjects and COPD Severity	Country	Measures	Quality	Detailed Description	Results
Seemungal et al., 2000 [12]	*N* = 101 severe COPD	United Kingdom	PEFR FEV_1 Symptoms	**Moderate quality**	**Period**: 2.5 years. PEFR and symptoms measured daily, post morning medication. In a subgroup of 34, FEV_1 was measured	Analysis of 504 exacerbations: Lung function changed significantly on the day of onset ($p < 0.001$). A decrease in the median of: PEFR by 8.6 L/m FEV_1: 24.0 mL FVC: 76.0 mL
Cooper et al., 2009 [13]	*N* = 19 mild–severe COPD	United Kingdom	HR SpO_2% PEFR FEV_1 Symptoms	**High risk of bias**	**Period**: 4 months. Participants measured their vital signs and recorded their symptoms twice a week in the morning	Analysis of four exacerbations: Concluded that SpO_2% was the variable most closely associated with exacerbation but no statistical significance reported
Sund et al., 2009 [14]	*N* = 18 severe COPD	United Kingdom	FEV_1 Symptoms	**Low quality**	**Period**: 6 months. Daily electronic diary and performed three spirometry manoeuvres daily in the evening	Analysis of 75 exacerbations: 55 exacerbations were detected via tele-health (symptoms) and 6/55 exacerbations were detected via FEV_1 alone (p = not significant). Exacerbation detected via FEV_1 was defined as a 10% fall in FEV_1 for ≥2 consecutive days.
Hurst et al., 2010 [5]	*N* = 31 severe COPD	United Kingdom	HR SpO_2% PEFR Symptoms	**Moderate quality**	**Period**: 9 months. Daily paper diary cards	Analysis of 13 exacerbations: Variation was noted prior and during the onset of exacerbation in PEFR, HR, and SpO_2%. Maximal change in SpO_2% and HR occurred two days into exacerbation: SpO_2% had fallen by −1.24 SD, HR increased by +3.09 SD. Maximal change in PEFR occurred four days into exacerbation: −2.97SD Composite Score to detect exacerbation: AUC = 0.832, $p < 0.05$.
Jensen et al. in 2012 [15]	*N* = 57 moderate–severe COPD	Denmark	HR SpO_2% BP	**Moderate quality**	**Period**: 4 months. Daily diary cards	Analysis of 9 exacerbations: Their algorithm classified variables into 273 features and was able to detect seven exacerbations via vital signs with 70% sensitivity, 95% specificity, AUC = 0.73.

Table 1. *Cont.*

Author	Subjects and COPD Severity	Country	Measures	Quality	Detailed Description	Results
Berge et al., 2012 [16]	*N* = 137 severe COPD	Netherlands	Salbutamol use PEFR Symptoms	**Moderate quality**	**Period**: 15 months. Daily diary cards	Analysis of 101 exacerbations: Significant decrease in PEFR 15 L/min at exacerbation compared to baseline.
Yanez et al. in 2012 [17]	*N* = 89 severe COPD (On O_2 therapy)	Spain	Respiratory Rate (RR)	**Moderate quality**	**Period**: 3 months. Daily monitoring of respiratory rate, using a sensor inserted into the domiciliary oxygen supply system	Analysis of 10 exacerbations: Increase in the mean respiratory rate in 21/30 exacerbations, 1–5 days prior to hospitalisation Mean of respiratory rate raised: Five days: 15.2 ± 4.3 min^{-1} to 19.1 ± 5.9 min^{-1} Two days: 2.3 min^{-1} (15% from baseline) One day: 4.4 min^{-1} (30% from baseline) All *p*-value < 0.05
Martin Lesende et al. 2013 [18]	*N* = 58 Heart failure (27.6%) + O_2 therapy (57.1%) + moderate−very severe COPD and asthma 25.9%	Spain	HR SpO_2% BP RR Weight Temperature Symptoms	**High risk of bias**	**Period**: 12 months. Daily monitoring	In the five days preceding hospital admission: Mean SpO_2% fell from 93.1% to 91.0% (4.6 SD), and mean HR increased from 77.8 to 84.2 min^{-1} (17.1 SD) $p = 0.003$ for both. No significant change for respiratory rate, body temperature and blood pressure.
Pedone et al. 2013 [19]	*N* = 99 moderate−severe COPD	Italy	HR SpO_2% TemperaturePhysical activity	**High risk of bias**	**Period**: 9 months. Automatic recording of vital signs, a mean of four times per day.	Analysis of 13 exacerbations: SpO_2% fell three days before an exacerbation, which permitted timely intervention, and was associated with a 33% reduction in hospitalisation rate (p = not shown, data displayed in a Figure only).
Segrelles et al., 2014 [7]	*N* = 60 severe COPD (On O_2 therapy)	Spain	HR SpO_2% BP PEFR	**High risk of bias**	**Period**: 7 months. Participants monitored their vital signs every morning, but PEFR was three times/week.	Analysis of 50 red flags: confirmed red flag defined as moderate, severe or very severe exacerbation. Tele-health was associated with significant reduction in acute NIV usage ($p < 0.0001$), ER visits ($p = 0.001$), admissions ($p = 0.015$) and bed days ($p = 0.018$). Reported that SpO_2% and PEFR were the most predictive parameters (but data not reported).

Table 1. *Cont.*

Author	Subjects and COPD Severity	Country	Measures	Quality	Detailed Description	Results
Harding et al., 2015 [20]	*N* = 18 moderate–very severe COPD	United Kingdom	HR SpO_2% Symptoms	**Moderate quality**	**Period**: 6 months. Each participant asked to fill a daily symptom diary card.	Analysis of 37 exacerbations: 15/37 exacerbations were identified in three days prior to medication self-initiation.Alerts related to events: 47 symptom alerts (16 patients) 80 HR alerts (18 patients), and 62 SpO_2% alerts (17 patients). *p* = not shown.
Mohktar et al., 2015 [21]	*N* = 21 moderate–very severe COPD	Australia	HR SpO_2% BP RR Weight Temperature FEV_1 Symptoms	**Moderate quality**	**Period**: 11 months. Participants daily monitored their vital signs and symptoms	Analysis of 90 exacerbations: The designed algorithm identified 55/90 true exacerbations (71.8% sensitivity 80.4% specificity). FEV_1 value (k = 0.21), mean of distribution of SpO_2% (k = 0.27) and the weight (k = 0.21) were the most predictive variables (*p* = not shown).
Fernandez-Granero et al., 2015 [22]	*N* = 16 severe–moderate COPD	Spain	Respiratory sound	**Moderate quality**	**Period**: 6 months. Daily recorded respiratory sounds using a microphone over the super-sternal notch	Analysis of 33 exacerbations: 25 out of 33 exacerbations were detected 5 ± 1.9 days prior to the onset of exacerbation by changes in sounds (*p* = not shown).
Burton et al., 2015 [23]	*N* = 33 mild–very severe COPD	United Kingdom	HR SpO_2% FEV_1 PEFR Symptoms	**Moderate quality**	**Period**: >200 days. Each participant asked to fill a symptom questionnaire, and measure heart rate, and SpO_2% daily. FEV_1 and PEFR monitored weekly.	Analysis of 172 exacerbations: Increase in HR (87 min^{-1}–94 min^{-1}) at the onset of exacerbation and mean SpO_2% fell (93.6% to 92.4%) around the onset of exacerbation. Exacerbation associated with a reduction of 0.1 L in FEV_1.
Borel et al., 2015 [24]	*N* = 44 severe COPD (On NIV and O_2 therapy)	France	RR %Triggering NIV usage Questionnaire	**Moderate quality**	**Period**: 6 months. Daily monitoring via the ventilator and daily EXACT-Pro questionnaire.	Analysis of 21 exacerbations: 21 exacerbations detected, and the risk of exacerbation was high if high value noted on $\geq$ two days out of five for RR P = 0.01, and %Triggered Breaths *p* = 0.037, but not total NIV usage *p* = 0.097).
Hamad et al., 2016 [25]	*N* = 183 COPD *	United Kingdom	HR SpO_2% Temperature Physical activity Symptoms	**Moderate quality**	**Period**: 4 months. Daily monitoring.	Analysis of 98 exacerbations: 80/98 showed changes on one or more tele-health parameters prior to hospitalisation/exacerbation onset. 30 exacerbations resulted in hospitalisation and 7/30 had significant SpO_2% reduction (significant defined for each patient individually, *p* = 0.049) 12/98 exacerbations had a significant SpO_2% fall ($p < 0.05$).

* Disease severity not reported. COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; PEFR: peak expiratory flow rate; FEV_1 forced expiratory volume in one second; HR: heart rate; SpO_2%: peripheral capillary oxygen saturation; BP: blood pressure; RR: respiratory rate; NIV: noninvasive ventilation; EXACT: exacerbations of chronic pulmonary disease tool; Pro: Patient-reported outcome; SD: standard deviation; AUC: area under the curve.

Table 2. Detailed description of the 16 included studies.

Author	Definition of Exacerbation
Seemungal et al., 2000 [12]	Anthonisen criteria.
Cooper et al., 2009 [13]	Not explained.
Sund et al., 2009 [14]	Increase of two symptoms and/or $\geq$10% reduction of FEV_1 for $\geq$2 consecutive days; or the use of antibiotics and/or prednisolone.
Hurst et al., 2010 [5]	$\geq$2 of new or worsening symptoms (one should be increased breathlessness, sputum volume of sputum purulence) for $\geq$2 days.
Jensen et al. in 2012 [15]	Admission to hospital, or started antibiotics or steroids with specific symptoms.
Berge et al., 2012 [16]	Not explained.
Yanez et al., 2012 [17]	Clinical diagnosis by an emergency room clinician.
Martin Lesende et al., 2013 [18]	Not explained.
Pedone et al., 2013 [19]	Change in symptoms that lead to a change in medication.
Segrelles et al., 2014 [7]	GOLD definition.
Harding et al., 2015 [20]	Initiation of antibiotics or steroids or both.
Mohktar et al., 2015 [21]	GOLD definition.
Fernandez-Granero et al., 2015 [22]	Use of medication for exacerbation, and/or unplanned emergency room visits and/or hospital admissions.
Burton et al., 2015 [23]	Anthonisen criteria or started antibiotics.
Borel et al., 2015 [24]	If abnormal values of respiratory rate and % triggered breaths were reported for two days or more, or abnormal values of NIV daily usage were reported for three days or more out of five. Abnormal values were defined as "value of a parameter was >75th or <25th percentile, the day was recorded as abnormal value' ('high value' > 75th, 'low value' < 25th).
Hamad et al., 2016 [25]	Admission to hospital, or started antibiotics or/and steroids.

3. Results

The systematic review search generated 3377 articles, 345 were excluded due to duplication. After screening the titles and abstracts, 28 articles out of 3032 were potentially relevant to the inclusion criteria. After that, full-text screening of the 28 articles was conducted to assess eligibility, which resulted in 13 relevant articles. The reference list of the relevant articles was also examined which resulted in identification of three further articles giving 16 in total (Figure 1).

Of the 16 articles that met the pre-specified inclusion criteria, all the studies were conducted prospectively, and in seven different countries: one each in Australia, Denmark, France, Italy, Netherlands, four in Spain, and eight in the United Kingdom. Most of the articles were published in 2015 (5/16), with three in 2012, two each in 2009 and 2013, and one each was published in 2000, 2010, 2014 and 2016. The sample size and duration of the studies varied from three months to fifteen months except for one study, which was run for 30 months. The sample size varied from 16 to 183 participants (eight studies <50 patients, five studies $\geq$50 patients, and three studies >100 patients). Fifteen studies were on COPD patients only (at different disease stages), and one was on heart failure and chronic lung disease patients [16]. Full details of the included studies are reported in Tables 1 and 2.

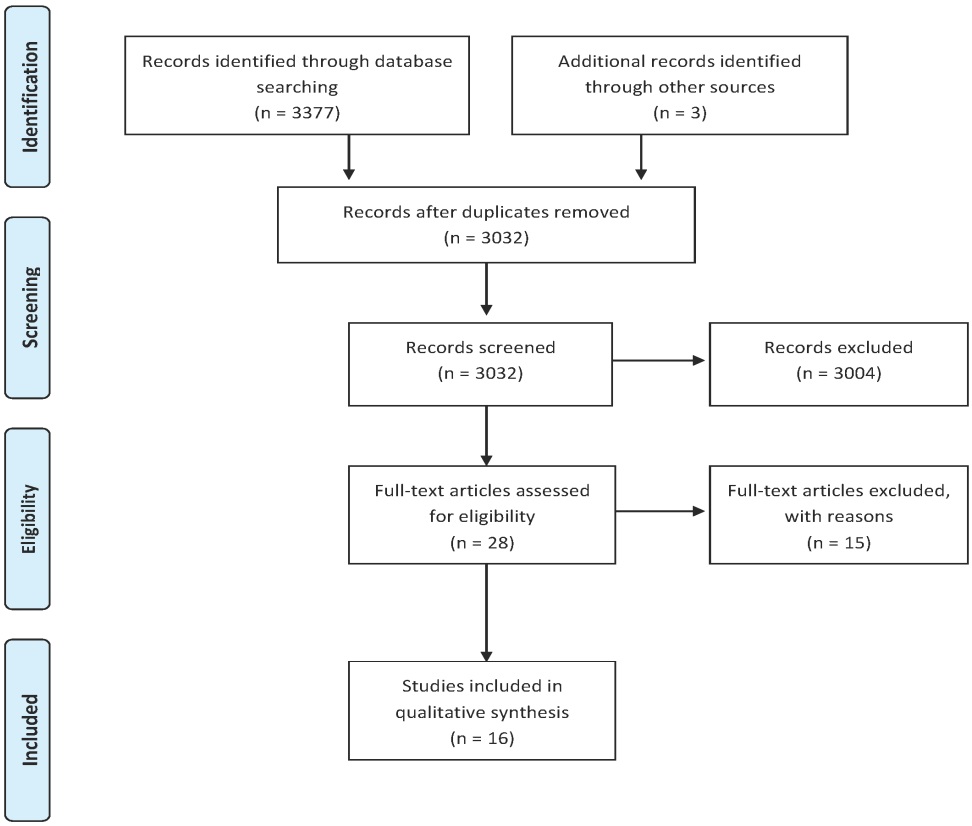

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram.

Quality Assessment

Among the 16 identified articles, four studies were randomised clinical trials and 12 were cohort studies. The four studies evaluated using the modified Cochrane risk of bias tool [10] were ranked as being at high risk of bias. The 12 studies evaluated by the modified Newcastle-Ottawa scale [11] were all ranked as moderate quality except for one, which was ranked as low quality.

4. Monitoring Vital Signs to Predict Exacerbation

4.1. Heart Rate and Oxygen Saturation

Most of the included studies 14/16 monitored the participant's vital signs and assessed the capability of vital signs to predict COPD exacerbation. Although heart rate (HR) and oxygen saturation (SpO_2%) were monitored in 10/16 studies [5,7,13,15,18–21,23,25], 7/10 studies did not report any statistical analysis for the HR and SpO_2% variation. However, they concluded with the possibility that heart rate and/or SpO_2% may be useful in detecting deterioration. Four studies (three at moderate quality, and one at high risk of bias) reported a significant variation ($p \leq 0.05$) in HR and/or SpO_2% prior to the onset of COPD exacerbation [5,18,23,25]. In Hurst et al. [5], the magnitude of the fall in SpO_2% two days into the exacerbation was −1.24 standard deviation (SD) and the rise in HR was +3.09 SD above the patient's baseline. Martin-Lesende et al. [18] reported the difference between the mean values monitored over the whole study period, which were for SpO_2% 93.1% (2.2 SD), and for HR 77.8 min^{-1} (14.6 SD); Moreover, the mean values monitored over the five days prior to cause-specific

admission were for SpO_2% 91.0% (4.6 SD) and for HR 84.2 min^{-1} (17.1 SD), $p = 0.003$ for both. There was therefore a typical rise in HR of 7 min^{-1} and fall in SpO_2% of 2%. Burton et al. [23] reported that the magnitude of SpO_2% fall and HR rise was approximately 1 SD (SpO_2% fall from 93.6% to 92.4%, and HR increased from 87.4 min^{-1} to 93.7 min^{-1}).

4.2. Respiratory Rate

The works of Yanez and Borel, which were ranked as moderate quality [17,24], evaluated variations in respiratory rate prior to an exacerbation. In both, the change was statistically significant ($p \leq 0.05$). Importantly Yanez et al. reported an increase in the mean respiratory rate one to five days prior to hospitalisation due to an acute exacerbation. At 48 h, the mean respiratory rate increased by 2.3 min^{-1} (15% from baseline) with 72% sensitivity and 77% specificity (area under the curve (AUC) = 0.76, $p < 0.05$) for detecting exacerbation, whilst the rise noted 24 h prior to hospitalisation at 4.4 min^{-1} (30% from baseline) had a 66% sensitivity and 93% specificity (AUC = 0.79, $p < 0.05$) for exacerbation detection. At five days before hospitalisation, the mean respiratory rate rose from 15.2 $\pm$ 4.3 min^{-1} to 19.1 $\pm$ 5.9 min^{-1} ($p < 0.05$) suggesting a longer window for preventing hospitalisation. However, in contrast, Martin Lesende [18] did not see significant change in the respiratory rate five days before hospitalisation. Mohktar [21] included respiratory rate with daily monitored variables, but no analysis was reported.

4.3. Blood Pressure and Temperature

Four studies of 16 (two at high risk of bias and two at moderate quality) included blood pressure monitoring [7,15,18,21], but there was no evidence indicating changes in blood pressure was as a variable with high predictive capacity for exacerbation (p-value not significant). Likewise, body-temperature was monitored in 4 out of of 16 studies. Martin-Lesende [18] compared the mean temperature in the overall follow-up period, 35.9 °C (0.4SD), to the mean of five days, 35.5 °C (1 SD), prior to cause-specific admission. Changes in body temperature resulted in 27.8% of alerts (only 5.6% of alerts were due to an increased temperature over 37 °C). Hamad [25] reported increased body-temperature in 9 out of 98 exacerbations.

Five studies (two at high risk of bias and three at moderate quality) out of 16 [13,15,19,20,22] did not provide sufficient statistical analysis of changes in vital signs despite reporting these variables. For example, Pedone [19] evaluated the capability of a tele-monitoring system for lower hospitalisation rates, and to identify COPD exacerbation onset. The researchers did not report whether the result was statistically significant but noted a 33% reduction in the risk of hospitalisation. Pedone also noted a fall in SpO_2% in three days preceding the onset of an exacerbation, which therefore led to prediction of COPD exacerbation. Furthermore, Jensen [15] tried to develop an algorithm to enhance the prediction of COPD exacerbation. The four variables heart rate, systolic blood pressure, diastolic blood pressure, and oxygen saturation were monitored and classified into 273 features. Jensen reported that their system was able to distinguish ten COPD exacerbations with 70% sensitivity, 95% specificity, and 0.73 AUC.

Considered together, SpO_2% was the most studied variable before an exacerbation episode, and the variable which has been reported to have the highest predictive capacity although the magnitude of change is typically small (1%–2%).

5. Monitoring Lung Function to Predict Exacerbations

Lung function, particularly spirometry, is a valuable test for diagnosing COPD and evaluating disease progression. A few studies assessed the usefulness of lung function variables in predicting acute exacerbation. Eight studies (two at high risk of bias, one as low quality, and two at moderate quality) of 16 [5,7,12–14,16,21,23] monitored either the peak expiratory flow rate (PEFR), or the forced expiratory volume in one second (FEV_1), or both. Three studies [12,13,23] measured FEV_1 and PEFR at different frequencies (per day/per week). Seemungal et al. [12] reported data from 101 COPD patients

on PEFR, FEV_1 and vital capacity (FVC) on the day of exacerbation onset, and showed significant changes ($p < 0.001$). The analysis of 504 COPD exacerbations revealed a fall in the median PEFR of 8.6 (interquartile range (IQR) 0 to 22.9) L/min, FVC of 76.0 (IQR −40.4 to 216.4) mL, and FEV_1 of 24.0 (IQR −16.1 to 84.3) mL. Burton et al. [23] reported a strong correlation between FEV_1 and PEFR and a 0.1 L reduction in FEV_1 was associated with a change in the symptom score.

Sund et al. at low quality and Mohktar et al. at moderate quality [14,21] focused only on FEV_1. Sund [14] detected 55/75 exacerbations using monitoring, and 6/55 exacerbations were detected only via FEV_1 (defined as a 10% fall in FEV_1 for $\geq$2 consecutive days). Three studies [5,7,16] examined predicting COPD exacerbations with daily monitoring of PEFR. Segrelles [7] did not report detailed PEFR data, but reported that PEFR and SpO_2% were the most predictive variables. Hurst [5] reported a statistically significant variation in PEFR before and during an acute exacerbation with a maximal −2.97 SD fall in PEFR four days into the exacerbation. However, Berge [16] reported a significant decrease in the mean of PEFR during an exacerbation episode, which was back to baseline in two weeks.

6. Monitoring Respiratory Sounds to Predict Exacerbations

In 2015 Fernandez-Granero at moderate quality [22] reported a study demonstrating that 25 out of 33 COPD exacerbations could be detected via monitoring patient's respiratory sounds at home. Each participant was asked to record his/her respiratory sounds daily by placing a microphone on the suprasternal notch. Exacerbation episodes were detected 5 ± 1.9 days prior to the exacerbation onset with a sensitivity of 73.76% and 97.67% specificity.

7. Methodological Considerations

7.1. Alarm limits

A challenge in COPD is the variation between patients and how to set alarm limits for an individual patient. Of the 16 articles included in this review, only eight studies (three at high risk of bias, one at low quality and two at moderate quality) [5,13,14,18–21,25] mentioned that they had customised the alarm limits for each individual. Methods used were reported in six out of the eight studies. Cooper [13] monitored the participants for two weeks to identify the normal range for each and personalise the alert limits. Sund [14] set a baseline for each participant by taking the median and the mean after monitoring symptoms and FEV_1 for 14 days (exacerbation-free). In the Hurst study [5], heart rate, oxygen saturation, and peak expiratory flow rate assessed for 30 days (symptom-free). These established a baseline of the selected variables with ±SD. Pedone [19] customised the limits based on the participant's "clinical situation". Harding [20] personalised each participant's limits by applying a probability density function after monitoring the participant for six weeks, or having 40 sets of recorded daily data. Mokhtar [21] personalised the limits range in a different way; they took the median (50th percentile), lower (25th percentile), and upper (75th percentile). They then adjusted the lower limits to be 25th percentile minus 1.5 times the interquartile, and the upper limits to be 75th percentile plus the 1.5 times the interquartile. There are no studies comparing different methods of personalising alarm limits.

7.2. Monitoring Characteristics

The approach pursued by the 16 studies in monitoring physiological signs were heterogeneous with regard to the type of equipment or instrument used to monitor and assess the participant's data. In some studies, a mobile/tablet app was used to communicate with the participant [19,20], and transfer data. Some studies set up a monitoring station for each individual with different devices [7,13–15,17–19,21–25], where the data were transmitted automatically through an Internet modem. If a red flag was raised or threshold breached, a notification alert was sent to the system operator in real time. In two other studies, another form of monitoring was used. A diary card

for symptoms and vitals were provided to participants, and a visit was arranged to collect the data [5,12,16].

7.3. Intermittent vs. Continuous Monitoring

In the reviewed articles, 16 studies monitored the participants' physiological parameters and symptoms intermittently. The frequency of monitoring/recording was varied, some once daily or multiple times daily. However, in four studies [7,13,14,23], participant's data were monitored less than daily (different frequencies per week). In addition to that, sometimes measurements taken were restricted to morning, however, in Harding et al. [20], the stipulated time for measurements recording was based on the patient's preference.

8. Discussion

We have conducted the first systematic review examining the utility of monitoring physiological variables to predict exacerbations of COPD. In general, and as discussed below, the studies are small and heterogeneous using different variables and different protocols. The need for better healthcare solutions in people diagnosed with chronic diseases is real. COPD imposes burdens on individuals and health care organisations. Whilst the methods hold promise, further adequately powered studies are required to properly define the utility of physiological monitoring to predict exacerbations.

In this systematic review, sixteen articles met the inclusion criteria, which were compliant with PRISMA. Five studies out of 16 [13,15,19,20,22] did not provide sufficient statistical data to draw conclusions consistent with the results of other studies, despite reporting changes in physiological variables (no p-value). The methodological quality of the studies was variable but generally low with 12 cohort studies ranked as moderate or low quality, and four trials ranked as having a high risk of bias.

We have described those studies that showed positive results in predicting/detecting an exacerbation episode via monitoring of physiological parameters. Although this approach appears to be promising, further well-designed clinical trials are required to investigate the true magnitude and time-course pre, during, and post an exacerbation episode of changes in physiological parameters. Understanding the extent of the magnitude of change for each variable is critical in using this knowledge for early exacerbation detection. In three studies [5,18,23] the magnitude of the change in heart rate and SpO_2% reported was an increase of around 5 min^{-1} for heart rate and a fall by 1%–2% for SpO_2%. Two studies [17,24] reported an increase in the respiratory rate before the onset of COPD exacerbation/hospitalisation. These findings all support the hypothesis that monitoring of vital signs can detect respiratory deterioration. However, the question arises as to whether these variables can be reliable enough. Moreover, to answer that question we need to better understand the relationship between physiological signs and symptoms. This has been confirmed in some of the above mentioned studies [5,12,14]. Hurst combined peak expiratory flow (PEF) with a symptom score to provide optimal exacerbation detection [5].

Having demonstrated that monitoring physiological variables has the theoretical potential to detect COPD exacerbations, the second step is implementation of this in a clinical environment—Tele-monitoring. To enable healthcare providers and patients to feel secure managing COPD and detecting acute exacerbations with no anticipated harm, an intelligent interface to provide live communication is essential. In the above mentioned studies, various designs were employed. However, the optimal technique/algorithm still requires more investigation. Despite the fact that tele-health offers the possibility for the clinician and the patient to be connected and monitored in a 'virtual clinic', the accuracy and specificity of this discipline are still uncertain. Developing an algorithm to detect an exacerbation is important because that would facilitate the services provided via tele-health. A particular challenge is around alarm thresholds. To increase the value of tele-health in self-management, a customised threshold for each patient is essential as this will help to decrease false alarms, and differentiate between true deterioration and day-to-day variation. Six studies had

addressed this issue by specifying the alarm settings for each individual [5,13,14,19–21], but using different methods and the optimal way to set individual patient alarms remains an open question.

Even though most of the reviewed studies exhibited some significant positive results in the efficacy of physiological parameters in predicting/detecting COPD exacerbation, there are insufficient data to draw a secure conclusion in this review. This is due to the diversity of the designs, methods, and sample size of studies. The demand for technology to meet the needs of the COPD patient and society are increasing. Further clinical trials are needed to achieve that.

Strength and Limitations

In this systematic review, a number of limitations can be considered. First, non-English studies (abstract and full text) were excluded. Second, only one author performed the screening of titles and abstracts, which may have increased the risk that studies were excluded inappropriately. Thirdly, the definitions of exacerbation vary across the studies, which can make comparison between studies challenging. The major strength of this study is that, to our knowledge, there is no pre-existing review conducted regarding the usefulness of monitoring physiological signs to predict COPD exacerbation.

9. Conclusions

Monitoring of physiological parameters may be useful in assisting earlier detection of COPD exacerbations but further, robust studies are required to confirm this. A particular challenge is how to set alarm limits for individual patients given the heterogeneity inherent in COPD and COPD exacerbations.

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Author Contributions: Al Rajeh and Hurst conceived and designed the study. Al Rajeh performed the initial search and data extraction, while Hurst checked the eligibility of included articles. Both authors performed the analysis, interpretation, and evaluation of data for each study. Al Rajeh wrote the manuscript draft and Hurst revised it. All authors read and approved the final manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix

Table A1. Medline Search Strategy.

1	lung diseases, obstructive/ or exp. bronchitis/ or exp. pulmonary disease, chronic obstructive/	84,036	Advanced	Display Results More
2	emphysema$.mp.	31,994	Advanced	Display Results More
3	bronchiti$.mp.	30,780	Advanced	Display Results More
4	(obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.	96,121	Advanced	Display Results More
5	(copd or coad or cobd or aecb).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	33,479	Advanced	Display Results More
6	1 or 2 or 3 or 4 or 5	153,864	Advanced	Display Results More
7	telemedicine/ or telerehabilitation/	14,118	Advanced	Display Results More
8	(telemonitor* or tele-monitor* or tele-health* or telehealth* or telemedicine or tele-medicine or tele-rehabilitat* or telerehabilitat*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	18,772	Advanced	Display Results More

Table A1. *Cont.*

9	(e-health or ehealth or m-health or mhealth or mobile health).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	8219	Advanced	Display Results More
10	exp. Telemetry/	10,614	Advanced	Display Results More
11	(telemetr* or tele-metr*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	12,888	Advanced	Display Results More
12	Monitoring, Ambulatory/	6635	Advanced	Display Results More
13	(monitoring adj4 (ambulatory or home$)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	23,156	Advanced	Display Results More
14	Domiciliary.mp.	2364	Advanced	Display Results More
15	software/ or mobile applications/ or user-computer interface/	114,192	Advanced	Display Results More
16	(software* or app? or iphone or ipad or android or smartphone* or smart-phone*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	205,344	Advanced	Display Results More
17	or/7–16	284,600	Advanced	Display Results More
18	(exacerbat* or deteriorat*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	176,862	Advanced	Display Results More
19	heart rate/	149,127	Advanced	Display Results More
20	Pulse/	16,765	Advanced	Display Results More
21	((heart* or pulse* or cardiac) adj3 rate*).mp.	229,964	Advanced	Display Results More
22	respiratory rate/ or Respiration/	75,932	Advanced	Display Results More
23	((respirat* or breath*) adj3 rate*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	24,774	Advanced	Display Results More
24	exp. Oximetry/	13,116	Advanced	Display Results More
25	oximetr*.mp.	15,161	Advanced	Display Results More
26	Oxygen/	150,124	Advanced	Display Results More
27	SPO_2.mp.	3207	Advanced	Display Results More
28	oxygen.mp.	519,842	Advanced	Display Results More
29	(physiological adj4 (variable* or measure*)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	10,547	Advanced	Display Results More
30	early diagnosis/	19,913	Advanced	Display Results More
31	(early adj4 (detect* or diagnos*)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	176,122	Advanced	Display Results More
32	predict*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1,238,846	Advanced	Display Results More
33	or/18–32	2,291,354	Advanced	Display Results More
34	6 and 17 and 33	795	Advanced	

Table A2. Database Search Strategy.

Database	Subject Heading	Keyword
Medline	lung diseases, obstructive/ or exp. bronchitis/ or exp. pulmonary disease, chronic obstructive/ telemedicine/ or telerehabilitation/ exp. Telemetry/ Monitoring, Ambulatory/ software/ or mobile applications/ or user-computer interface/ heart rate/ Pulse/ respiratory rate/ or Respiration/ exp. Oximetry/ Oxygen/ early diagnosis/	emphysema$. bronchiti$. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)). (copd or coad or cobd or aecb) (telemonitor* or tele-monitor* or tele-health* or telehealth* or telemedicine or tele-medicine or tele-rehabilitat* or telerehabilitat*) (telemetr* or tele-metr*) (monitoring adj4 (ambulatory or home$)). Domiciliary. (software* or app? or iphone or ipad or android or smartphone* or smart-phone*). (exacerbat* or deteriorat*). ((heart* or pulse* or cardiac) adj3 rate*). ((respirat* or breath*) adj3 rate*). oximetr*. SPO_2. oxygen. (physiological adj4 (variable* or measure*)). (early adj4 (detect* or diagnos*)). predict*.
Embase	lung diseases, obstructive/ or exp. bronchitis/ or exp. pulmonary disease, chronic obstructive/ exp. telemonitoring/ or exp. telemedicine/ telerehabilitation/ exp. telephone telemetry/ or exp. telemetry/ exp. ambulatory monitoring/ computer program/ or exp. communication software/ or exp. mobile application/ exp. computer interface/ heart rate variability/ or exp. heart rate/ exp. pulse rate/ or exp. “heart rate and rhythm”/ exp. breathing/ or exp. breathing rate/ exp. oximetry/ or exp. measurement/ or exp. pulse oximetry/ exp. oxygen breathing/ exp. early diagnosis/	emphysema$. bronchiti$. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)). (copd or coad or cobd or aecb). (telemonitor* or tele-health* or telehealth* or telemedicine or tele-medicine or tele-monitor*). (e-health or ehealth or m-health or mhealth or mobile health). (telemetr* or tele-metr*). ((respirat* or breath*) adj3 rate*). oximetr*. SPO_2. Oxygen (physiological adj4 (variable* or measure*)). (early adj4 (detect* or diagnos*)). predict*. (monitoring adj4 (ambulatory or home$)). Domiciliary. (software* or app? or iphone or ipad or android or smartphone* or smart-phone*). (exacerbat* or deteriorat*). ((heart* or pulse* or cardiac) adj3 rate*).
AMED	pulmonary disease chronic obstructive/ or bronchitis/ or pulmonary emphysema/ or lung diseases obstructive/ telemedicine/ home care services/ internet/ or exp. computers/ or software/ disease progression/ heart rate/ Pulse/ exp. Respiration/ Oxygen/ monitoring physiologic/ or respiratory function tests/ diagnosis/	emphysema$. bronchiti$. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)). (copd or coad or cobd or aecb). (telemonitor* or tele-monitor* or tele-health* or telehealth* or telemedicine or tele-medicine or tele-rehabilitat* or telerehabilitat*). (e-health or ehealth or m-health or mhealth or mobile health). (telemetr* or tele-metr*). ((monitoring adj4 (ambulatory or home$)). Domiciliary. (software* or app? or iphone or ipad or android or smartphone* or smart-phone*). (exacerbat* or deteriorat*). ((heart* or pulse* or cardiac) adj3 rate*). ((respirat* or breath*) adj3 rate*). oximetr*. SPO_2. oxygen. (physiological adj4 (variable* or measure*)). (early adj4 (detect* or diagnos*)). predict*.

Table A2. *Cont.*

Database	Subject Heading	Keyword
CINAHL	(MH "Lung Diseases, Obstructive") OR (MH "Bronchitis+") OR (MH "Emphysema") OR (MH "Pulmonary Disease, Chronic Obstructive+") (MH "Telenursing") OR (MH "Telepathology") OR (MH "Remote Consultation") OR (MH "Telemedicine") OR (MH "Telehealth") (MH "Telemetry") (MH "Ambulatory Care") (MH "Software") OR (MH "Communications Software+") OR (MH "Mobile Applications") OR (MH "User-Computer Interface+") (MH "Pulse") OR (MH "Heart Rate") (MH "Wireless Communications") OR (MH "Telephone+") OR (MH "Instant Messaging") (MH "Respiratory Rate") OR (MH "Respiratory Sounds") (MH "Respiration+") (MH "Oximetry+") (MH "Oximeters+") (MH "Oxygen") (MH "Oxygenation") OR (MH "Oxygen Saturation") (MH "Monitoring, Physiologic") (MH "Early Diagnosis")	TX emphysema* TX bronchiti* TX (copd or coad or cobd or aecb) TX (obstruct* n3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) TX (telemonitor* or tele-monitor* or tele-health* or telehealth* or telemedicine or tele-medicine or tele-rehabilitat* or telerehabilitat*) TX (e-health or ehealth or m-health or mhealth or "mobile health") TX (telemetr* or tele-metr*) TX monitoring n4 (ambulatory or home*) TX Domiciliary TX (app# or iphone or ipad or android or smartphone* or smart-phone*) OR TI software* OR AB software* TX (exacerbat* or deteriorat*) TX ((heart* or pulse* or cardiac) n3 rate*) TX (respirat* or breath*) n3 rate* TX oximetr* TX SPO_2 TX oxygen TX (physiological n4 (variable* or measure*)) TX (early n4 (detect* or diagnos*)) TX predict*
Cochran	[mh "lung diseases, obstructive"] [mh bronchitis] [mh "pulmonary disease, chronic obstructive"] [mh telemedicine] [mh telerehabilitation] [mh Telemetry] [mh "Monitoring, Ambulatory"] [mh software] [mh "mobile applications"] [mh "user-computer interface"] [mh "heart rate"] [mh pulse] [mh "respiratory rate"] [mh Respiration] [mh Oximetry] [mh Oxygen] [mh "early diagnosis"]	COPD emphysema* bronchiti* (obstruct* near/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) (copd or coad or cobd or aecb) (telemonitor* or tele-monitor* or tele-health* or telehealth* or telemedicine or tele-medicine or tele-rehabilitat* or telerehabilitat*) (e-health or ehealth or m-health or mhealth or mobile health) (telemetr* or tele-metr*) (monitoring near/4 (ambulatory or home*)) Domiciliary (software* or app or apps or iphone or ipad or android or smartphone* or smart-phone*) (exacerbat* or deteriorat*) ((heart* or pulse* or cardiac) near/3 rate*) ((respirat* or breath*) near/3 rate*) oximetr* SPO_2 Oxygen (physiological near/4 (variable* or measure*)) (early near/4 (detect* or diagnos*)) predict*

Table A3. Excluded Studies.

First Author	Study Title	Reason
Malliopoulos, C., 2008	Continuous mobile services for healthcare: The health wear project	Article not available and no response from the author
Antoniades, N.C., 2012	Pilot study of remote telemonitoring in COPD	No physiological data shown and it does not address the prediction of COPD exacerbation
Jensen, M.H., 2012	Clinical impact of home telemonitoring on patients with chronic obstructive pulmonary disease	Not relevant (evaluated the impact of tele-health on patients, not in predicting exacerbation)
Jakobsen, A.S., 2013	Hospital-admitted COPD patients treated at home using telemedicine technology in The Virtual Hospital Trial: methods of a randomized effectiveness trial	Recruited non-stable COPD patients for preventing readmission

Table A3. *Cont.*

First Author	Study Title	Reason
Jehn, M., 2013	Tele-monitoring reduces exacerbation of COPD in the context of climate change-a randomized controlled trial	Looked at the association between the weather and exacerbation.
Pinnock, H., 2013	Effectiveness of telemonitoring integrated into existing clinical services on hospital admission for exacerbation of chronic obstructive pulmonary disease: researcher blind, multicentre, randomised controlled trial	No physiological variation reported and not for predicting exacerbation
San Miguel, K., 2013	Telehealth remote monitoring for community-dwelling older adults with chronic obstructive pulmonary disease	No physiological variation reported and not for predicting exacerbation
Schou, Lone, 2013	A randomised trial of telemedicine-based treatment versus conventional hospitalisation in patients with severe COPD and exacerbation—Effect on self-reported outcome	Not for predicting exacerbation and recruited non-stable COPD patients
van der Heijden, M., 2013	An autonomous mobile system for the management of COPD	Designing a mobile system
Zhang, J., 2013	MIOTIC study: A prospective, multicenter, randomized study to evaluate the long-term efficacy of mobile phone-based internet of things in the management of patients with stable COPD	No physiological variation reported and not for predicting exacerbation
Ding, H., 2014	A pilot study of a mobile-phone-based home monitoring system to assist in, remote interventions in cases of acute exacerbation of COPD	Did not report any monitored physiological data
Ko, F.W.S., 2014	COPD care programme can reduce readmissions and in-patient bed days	Recruited non-stable COPD patients
Minami S., 2014	Ambulatory pulse oximetry monitoring in Japanese COPD outpatients not receiving oxygen therapy	Monitored the patient's SPO_2% for a 24 h period only.
Jakobsen, A.S., 2015	Home-Based Telehealth Hospitalization for Exacerbation of Chronic Obstructive Pulmonary Disease: Findings from "The Virtual Hospital" Trial	Recruited non-stable COPD patients
Ringbaek, T., 2015	Effect of telehealthcare on exacerbations and hospital admissions in COPD: A randomised controlled trial	No physiological variation reported and not for predicting exacerbation

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Appendix 9

EUROPEAN RESPIRATORY *journal*
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Patient specific parameter thresholding to support domiciliary monitoring in COPD

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Article | Figures & Data | Info & Metrics

Abstract

Introduction: Domiciliary monitoring is increasingly used in COPD. There is a trade off between the number of false-alarms raised by such systems and the sensitivity of the system to detect exacerbations. Arbitrary limits are often set, but we hypothesised that limits set for an individual patient based on an assessment of their own data would increase the sensitivity and specificity of monitoring. Here we report the effect on false-alarm calls. Based on the American guidelines, normal heart rate is 60 – 100 bpm and standard SpO2 is ≥ 95%.

Aim: Set the appropriate alarm limits to an individual patient to reduce the number of false alarms.

Method: In this pilot study, we recorded five weeks of HR and SpO2 %, data were collected once each day prospectively from 8 COPD patients from the domiciliary telehealth project following pulmonary rehabilitation. Data collected in the first two weeks were used to set the appropriate limits for each patient by calculating the mean and SD over that period, and setting the alarm at +/- 1.5 and 1.96 SD.

Result: The mean age of 8 Patients was 69.6 years (10.47 SD), 75% males, and FEV1% mean 42% (19.7 SD). The table shows the alarm frequency for each algorithm. Results are expressed as alarms/day. Setting alarms by individual parameters versus did not alter the frequency of HR alarms but reduced the frequency of SpO2 alarms.

HR 60 - 100 bpm	HR +/- 1.5 SD	HR +/- 1.96 SD	P = Kruksall Wallis	SpO2 95 - 98 %	SpO2 +/- 1.5 SD	SpO2 +/- 1.69 SD	P = Kruksall Wallis
0.13	0.15	0.07	0.343	0.28	0.02	0.02	0.046

Conclusion: In this study we show that alarm rates vary by arbitrary versus patient specific thresholding. We were able to decrease the false alarms and reduce the volume of calls on the team.

Telemedicine COPD - management Chronic disease

C24. NEW TECHNOLOGIES FOR MANAGING COPD

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Tele-Health with Chronic Obstructive Pulmonary Disease (COPD)

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C24 NEW TECHNOLOGIES FOR MANAGING COPD / Poster Discussion Session / Tuesday, May 22/9:15 AM-11:15 AM / Room 30 C-E (Upper Level) - San Diego Convention Center

Tele-Health with Chronic Obstructive Pulmonary Disease (COPD)

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Introduction: Tele-Health services are increasingly used to support the management of people living with Chronic Obstructive Pulmonary Disease (COPD). The primary purpose can vary from one provider to another, whilst the effectiveness of Tele-Health in COPD remains controversial. Thus, identifying the optimal methods to use Tele-Health could increase the efficacy of services. We hypothesised that methods used in the provision of Tele-Health for COPD patients will vary across the world, as will beliefs about the utility of Tele-Health amongst health-care professionals. We conducted a global survey on healthcare providers to examine this. Method: An electronic survey comprising of 14 questions was conducted on health care providers. The survey was focusing on the use of Tele-Health in COPD patients. Five different aspects were covered: purpose, equipment, selected variables, alarm setting, and perception. Result: 134 participants completed the survey from 28 countries (seven continents). Only 45 (34%) used Tele-Health in COPD. 42% were respiratory therapists, 29% doctors, 14% physiotherapists, and 14% nurses and miscellaneous. Of those who used Tele-Health, 61% used it for baseline monitoring, 50.1% for early detection of exacerbations, and 46% for monitoring recovery from an exacerbation. The equipment used (hardware) was reported as smartphones/tablet app (54%), fixed telephone (26%), monitoring station (18%) and video phone (7%). The variables being recorded are reported in Figure 1. With regard to the perception of providers, 59% thought their technique of setting alarm limits made the service more efficient with a mean score of seven on a Likert scale, and 62% thought their alarm technique was sensitive enough to identify an exacerbation. In general, 90% thought that Tele-Health was useful in COPD patients with a mean score of eight. Conclusion: Despite the lack of evidence to support use, there was widespread enthusiasm for Tele-Health in COPD with a belief that it can help detect exacerbations. Indications, hardware and the aspects of COPD that are monitored vary.