UNIVERSITY OF SOUTHAMPTON

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Risk prediction and modification in a clinical and database population of people with Chronic Obstructive Pulmonary Disease.

by

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Thesis for the degree of Doctorate of Medicine

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This thesis is dedicated to the memory of Mark Stafford-Watson, a committed advocate for all those living with chronic respiratory disease.

ABSTRACT

FACULTY OF MEDICINE

Thesis for the degree of Doctorate of Medicine

RISK PREDICTION AND MODIFICATION IN A CLINICAL AND DATABASE POPULATION OF PEOPLE WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

Lucy Anne Rigge

COPD is a leading cause of hospital admission and healthcare utilisation in the UK. The DOSE score can be used to risk stratify COPD patients based on clinical components routinely measured in Primary Care. Resource is often focussed on patients with high symptom burden, presenting repeatedly to medical professionals.

We hypothesised that a database approach could be used to identify lower risk COPD patients by DOSE score and a subgroup at higher risk of clinical deterioration could be further identified using their documented clinical characteristics. We hypothesised that early specialist clinical review of COPD patients would reduce their subsequent symptom burden and future health care utilisation.

In a real-world COPD database cohort of 13,608 Primary Care records, we risk stratified patients over four years by DOSE score. We showed clinical characteristics could identify a subgroup at increased risk of poor health outcomes with recent pneumonia and a raised eosinophil count showing the strongest individual associations. Logistic regression modelling determined the combination of characteristics most strongly associated with poor health outcomes.

In a feasibility study, 120 patients deemed low risk by DOSE score were identified by Primary Care electronic record search. 76 patients were randomised to an intervention of respiratory specialist review in their Primary Care Practice. The findings suggested that proactive speciality review in a modified form warrants further research with modification of endpoint measures and further development of the recruitment process to avoid recruitment bias.

In conclusion, we established the DOSE score can be administrated within a database approach and clinical characteristics can be used to further risk stratify COPD patients within a database. Pro-active specialist review of patients low risk by DOSE score is feasible for further study with some modification.

Table of Contents

List of Figures

List of Tables

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Declaration of Authorship

Print name:	Lucy Anne Rigge

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I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

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2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
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7. None of this work has been published before submission

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List of Abbreviations

ACOS	Asthma-COPD Overlap Syndrome
AE	Adverse Event
A fibrillation	Atrial fibrillation
BMI	Body Mass Index
BPH	Benign prostatic hypertrophy
CAD	Coronary artery disease
CAT	COPD Assessment Test
CHF	Congestive heart failure
CLAHRC	National Institute of Health Research, Collaborations for Leadership in Applied Health Research and Care
COPD	Chronic Obstructive Pulmonary Disease
CPFE	Combined Pulmonary Fibrosis and Emphysema
CRF	Chronic Renal Failure
CT	Computer Tomotography
CVA	Cerebrovascular accident
DJD	Degenerative Joint Disease
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GAD-7	The General Anxiety Disorder Assessment
GINA	Global initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GORD/GERD	Gastro-oesophageal reflux disease
GP	General Practitioner
HHR	Hampshire Healthcare Record
HHRA	Hampshire healthcare record Analytical Database
HIV	Human Immunodeficiency Virus

HTN	Hypertension
ICD	International Classification of Diseases
ICS	Inhaled corticosteroid
ICS/LABA	Combination inhaled corticosteroid and long acting β agonist
IPF	Idiopathic Pulmonary Fibrosis
IQR	Interquartile range
LABA	Long acting β agonist
LABA/LAMA	Combination long acting β agonist and long acting muscarinic antagonist
LAMA	Long acting muscarinic antagonist
mMRC	Modified Medical Research Council Breathless Score
MRC	Medical Research Council Breathless Score
NHS	National Health Service
NICE	National Institute of Clinical Excellence
OSA	Obstructive sleep apnoea
PAD	Peripheral arterial disease
PHQ-9	Patient health Questionnaire
QOF	Quality Outcomes and Framework
RHF	Right heart failure
SABA	Short acting β agonist
SAE	Serious Adverse Event
SAMA	Short acting muscarinic antagonist
SGRQ	St George's Respiratory Questionnaire
TRUD	Technology Reference Data Update Distribution

1 Introduction

1.1 Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable lung disease characterised by cough, sputum production and breathlessness [1]. It is caused by the inhalation of noxious particles, the most common cause being tobacco smoke [2].

Worldwide, COPD is the fifth leading cause of death [2, 3] and one of the top three non-communicable cause of death. Whilst the mortality rates from other leading causes of death continue to fall, the mortality rates from COPD continues to rise and is it projected to become the fourth overall leading cause of death worldwide by 2030 [1]. COPD was responsible for an estimated 4.2 million deaths worldwide in 2010, surpassed only by deaths from cardiovascular disease, cancer and infectious diseases [2].

There are approximately 3 million individuals in the UK living with COPD [4]. In England, COPD causes 25,000 deaths each year, accounting for 4.8% of all deaths. This is the second highest mortality rate (from lung and respiratory disease) in Western Europe [5, 6].The disease causes a substantial economic and symptom burden, estimated in 2010 to cost the NHS over £800 million each year and cause the loss of 24 million working days per annum (at a cost estimated to be £2.7 billion) [7]. In 2009-2010, COPD caused the second highest number of emergency admissions of any disease in the UK which resulted in over 1 million hospital bed days. Approximately a third of these patients were readmitted within 30 days and one in ten died during this readmission period [7]. These numbers have continued to increase with over 112,000 emergency COPD related hospital admissions in England during 2013- 2014 [6]. COPD prevalence is expected to rise over the coming decades due to continued exposure to COPD risk factors and an aging population, and, the economic and symptom burden is expected to rise accordingly [1].

Most cases of COPD worldwide are caused by cumulative years of exposure to inhaled smoke from tobacco or biomass fuels. Whilst tobacco smoking is the commonest cause of COPD and remains the causative agent in the vast majority of cases in the UK, the relationship is more complex than a simple correlation between increasing cumulative exposure and increasing disease severity with other genetic and environmental contributory factors [2].

The pathological process of airway obstruction is seen in a small but significant minority of those who have never smoked (never smokers). In addition, not everyone who smokes tobacco will develop COPD and the pattern and severity of disease varies from person to person, independent

of their smoke exposure. Increasing recognition is being given to the contribution from air pollutants in COPD which may take the form of occupational (workplace) exposure to organic and inorganic dusts, chemical agents and fumes [1]. In developed countries, it is estimated that between 10-20% of COPD symptoms may be accounted for by occupational sources. This contribution is likely to be higher in other areas of the world where the regulations surrounding working condition and air quality are less robust [2]. A significant contributor to air pollution is biomass fuels. Nearly three billion people worldwide cook over biomass fuels or coal and use it as their main heat source. The effect is attenuated by poorly ventilated buildings, putting this relatively small population at very high risk of lung damage[8]. Other inhaled substances such as marijuana and heroin are also risk factors for the development of COPD and cause increased disease severity and symptom burden when compared to tobacco smoke alone [9-11] . Exposure to environmental tobacco smoke (passive smoking) is likely to increase COPD risk although the relationship is not easily quantifiable [1].

The lung damage caused by heat and airborne particulate matter in COPD affects the lung tissue and the airways:

1. The airways are irritated by the airborne particles which causes them to become inflamed, to swell and stimulates excessive mucus secretion. This is part of the lung's normal defence mechanism but in COPD this appears to be attenuated and sparks a pathological process of chronic airways inflammation. The cilia within the airways may be immobilised or destroyed and the inflammatory cells produced altered or disabled, with the overall effect of narrowing the airways diameter, potentially breaching the lung's defence mechanism and irrevocably altering the airways anatomy, creating an ideal environment for bacteria and viruses to flourish[1, 12]
2. A proportion of the noxious particles in the inspired air will reach the alveolar tissue and here they act to destroy the membranes that create the alveolar walls. This causes large airspaces or holes to develop within the lungs, known as emphysema. Without sufficient alveolar membranes present, gas exchange may be inadequate, leading to tissue hypoxia (lack of oxygen) and hypercapnoea (carbon dioxide retention) [1, 12].
3. These structural changes at airway and alveolar level can lead to the loss of lung elastic recoil and damage the integrity of the airway walls causing them to collapse. These collapsed airways act as valves, allowing air into the emphysematous lung but not allowing it to escape. This causes the damaged, redundant, areas of the lung to overinflate, squashing the less damaged, functioning areas of lung tissue. This process is

known as air trapping or hyperinflation and further emphasises the effects of those metabolic problems previously described [1, 12].

1.2 The diagnosis and treatment of Chronic Obstructive Pulmonary Disease

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) is recognised as the leading international body in COPD expertise. GOLD was formed in 1998 by collaboration between the World Health Organisation and the National Heart, Lung and Blood Institute. The aim was to promote global awareness of COPD and to help alleviate the heavy symptom burden and high mortality rates seen at the time [13]. The GOLD guidelines were first published in 2001 and provide a 'Global strategy for the diagnosis, management, and prevention of Chronic Obstructive Lung Disease' available to all and regularly updated to incorporate the most recent evidence base [13].

The GOLD guidelines define COPD as *"a common preventable and treatable disease. characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases" [1].*

In accordance with the current GOLD guidelines, a diagnosis of COPD should be considered in all patients with a suggestive clinical history of chronic, progressive, cough, sputum production, dyspnoea and appropriate risk factors for the disease, but should not be confirmed without spirometric measurement of airflow limitation [1].

Spirometry is a simple, portable measure of exhaled air volumes. Key to a diagnosis of COPD is the measurement of the Forced Vital Capacity, FVC (the total amount an individual can exhale from full inspiration to full expiration) and the Forced Expiratory Volume in 1 second, FEV_1 (the amount an individual can blow out in the first second of the FVC, with maximal effort) [14]. In COPD, the pathological airway narrowing causes a disproportionately large decrease in the FEV_1 in comparison with the FVC, confirmed by an FEV_1/FVC ratio of less than 0.7. An FEV_1/FVC ratio of less than 0.7 is the spirometric definition of airway obstruction, seen in asthma, COPD and bronchiectasis [12]. However, unlike a diagnosis of asthma or bronchiectasis, a diagnosis of COPD requires obstructive spirometry in the presence of optimal pharmacological bronchodilation, hence the emphasis on *persistent* airflow limitation seen in the GOLD guidelines.

Periodic episodes of an increase in the level of inflammatory response seen in COPD are common and are characterised by an increase in cough, wheeze, breathlessness or sputum volume or a change in sputum colour and are termed 'exacerbations'. These episodes cause an increase in mucous secretion, airway narrowing and gas trapping all of which contribute to a further decrease in gas exchange. Exacerbations may be triggered by a viral or bacterial pathogen, a change in weather, air pollutants or the cause may be unknown [1]. The GOLD guidelines define an exacerbation 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" [1].

Not all patients with COPD will exacerbate and that there are different clinical phenotypes within COPD with different exacerbation rates is now widely accepted [8], but for those individuals that do exacerbate, the treatment and prevention of exacerbations is key to their management. Exacerbations have been shown to accelerate the rate of lung function decline [15], are the commonest cause of hospitalisation in COPD and are associated with increased mortality [16-18]. Standard pharmacological treatment of exacerbations involves appropriate antibiotics and oral corticosteroids, nebulised bronchodilators may also be appropriate dependent on the severity of the patients disease and exacerbation [1].

Management of COPD should encompass both pharmacological and non-pharmacological therapeutic strategies and should aim for symptom relief and modification of the risk to future lung health.

- Non-pharmacological treatment:
    - Smoking cessation is the intervention with the greatest effect on disease trajectory in COPD and consequently is considered the most important intervention for all COPD patients who continue to smoke [1]. Smoking cessation interventions have been shown to be most effective when a combination of psychological and pharmacological therapies are used [2].
    - Pulmonary rehabilitation is recommended for all COPD patients who are considered to have either high symptom levels or high levels of risk [1]. Pulmonary rehab has both education and exercise components and has been demonstrated to improve survival, hospitalisation rates, health-related quality of life, dyspnoea, anxiety and depression symptoms [19-21]. It is one of the strategies by which patients are encouraged and empowered to self-manage their condition.

- Vaccination against seasonal influenza strains and pneumococcus should be considered according to local public health guidance and is recommended for all COPD patients without contraindications in the UK [1].

- Pharmacological treatment: An inhaled long acting bronchodilator is recommended in all patients with symptomatic COPD. Those patients with two or more exacerbations a year, a hospital admission, or those who remain symptomatic on bronchodilation alone are recommended a combination inhaled corticosteroid/long acting B-agonist (ICS/LABA) to be taken concurrently with an inhaled long acting muscarinic antagonist (LAMA). Depending on the severity of their symptoms and disease patients may require additional oral or nebulised bronchodilators, mucolytic or palliative pharmacological symptom management with opiates and benzodiazepines [1].
- Other therapies including oxygen prescription, specialist respiratory psychological management, lung volume reduction surgical techniques, lung transplant and specialist palliative care may all be appropriate dependent on the individual patient's needs [1].

1.3 Measures of severity, prognosis and risk in COPD

In 2001 the first GOLD guidelines were produced and within them the first 'staging' system for COPD, (Table 1-1) based predominantly on spirometry values FEV_1 [13].

Table 1-1 The 2001 GOLD Spirometric Staging system [13].

Classification of Severity of COPD	
GOLD Spirometric Stage	**Characteristics**
GOLD 0: At risk	-normal spirometry -chronic symptoms (cough, sputum production)
GOLD I: Mild COPD	-FEV_1/FVC <70% -$FEV_1 \geq$ 80% predicted -with or without chronic symptoms
GOLD II: Moderate COPD	-FEV_1/FVC <70% - 30% ≤ FEV_1 <80% predicted -with or without chronic symptoms
GOLD III: Severe COPD	-FEV_1/FVC <70% - FEV_1 <30% predicted or FEV_1 <50% predicted plus respiratory failure of clinical signs of right heart failure

This system provided a standardised structure for severity grouping with regards to airways obstruction in COPD research, with the 'severe airways obstruction' reclassified as an $FEV_1 \leq 50\%$ but >30% and 'very severe airways obstruction' of $FEV_1 \leq 30\%$ predicted. Much is now known about the mortality risk and prognosis of those who fall into each of the FEV_1 category groups [8]. Figure 1-1, reproduced from the GOLD 2014 guidelines, summarises the research data from three

large research cohorts, TORCH [22], Eclipse [23] and Uplift [24]. It details the increased rate of exacerbation, hospitalisation and mortality seen as the spirometry stage becomes more severe.

Figure 1-1 Figure demonstrating exacerbation, hospitalisation and exacerbation rate by spirometric stage [8]

GOLD Spirometric Stage	Exacerbations (per year)	Hospitalisations (per year)	3-year Mortality
GOLD II: Moderate	0.7 – 0.9	0.11 – 0.2	11%
GOLD III: Severe	1.1 – 1.3	0.25 – 0.3	15%
GOLD IV: Very Severe	1.2 – 2.0	0.4 – 0.54	24%

As the field of COPD management has developed it has become increasingly recognised that whilst the FEV_1 provides useful clinical information, the patient population and disease course in COPD is physiologically diverse. FEV_1 is only a part of the clinical information needed to best guide individual patient management and consequently the spirometry classification within the GOLD guidelines is now referred to as a 'grading' rather than 'staging' system [8]. By 2014, treatment objectives in the 2014 GOLD guidelines were focussed not just on symptoms but also on their impact on the patient's quality of life [8].

The 2014 Gold Guidelines set out the following treatment guidelines [8]:

i. To relieve and reduce the impact of symptoms in the short term.
ii. Preventative strategies aimed at decreasing the future impact of the disease on the patient's health and quality of life.

The presence of individual symptoms such as cough or sputum production is easy to ascertain and record but the impact that symptom has on an individual's life is complex, very personal and far more difficult to quantify.

One of the first widely used symptoms scores was the British Medical Research Council's (MRC) breathlessness score, developed in 1960 [25] following the recognised need to standardise the recording of dyspnoea symptoms. The current Modified MRC (mMRC) score (Figure 1-2) demonstrates reasonable correlation with symptom burden and health related quality of life [26-29]. It has the advantage of being quick and easy to deliver and is widely known and understood in medical communities, however, given it only quantifies the impact of breathlessness on a patient's life it does not reflect the multifaceted symptom burden experienced by the individual COPD patient.

Figure 1-2 The Modified Medical Research Council Breathlessness score [8].

Modified Medical Research Council Questionnaire for Assessing the Severity of Breathlessness	
PLEASE TICK IN THE BOX THAT APPLIES TO YOU (ONE BOX ONLY)	
mMRC Grade 0. I only get breathless with strenuous exercise.	☐
mMRC Grade 1. I get short of breath when hurrying on the level or walking up a slight hill.	☐
mMRC Grade 2. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	☐
mMRC Grade 3. I stop for breath after walking about 100meters or after a few minutes on the level.	☐
mMRC Grade 4. I am too breathless to leave the house, or I am breathless when dressing or undressing.	☐

The St George's Respiratory Questionnaire (SGRQ) (www.healthstatus.sgul.ac.uk), developed in 1992 is a 50-item questionnaire which calculates a total score as well as sub-scores for three domains; symptoms, activity and impact. Used as a GOLD-standard in research and specialist respiratory settings, it is one of the most well evidenced and comprehensive ways of quantifying respiratory symptom burden and the consequent impact on quality of life in those with obstructive airways disease [30].The SGRQ has been shown to be strongly associated with exacerbation frequency, mortality and quality of life [31-35]. It correlates well with FEV_1, 6-minute walk test, MRC score and measures of anxiety and depression [36].

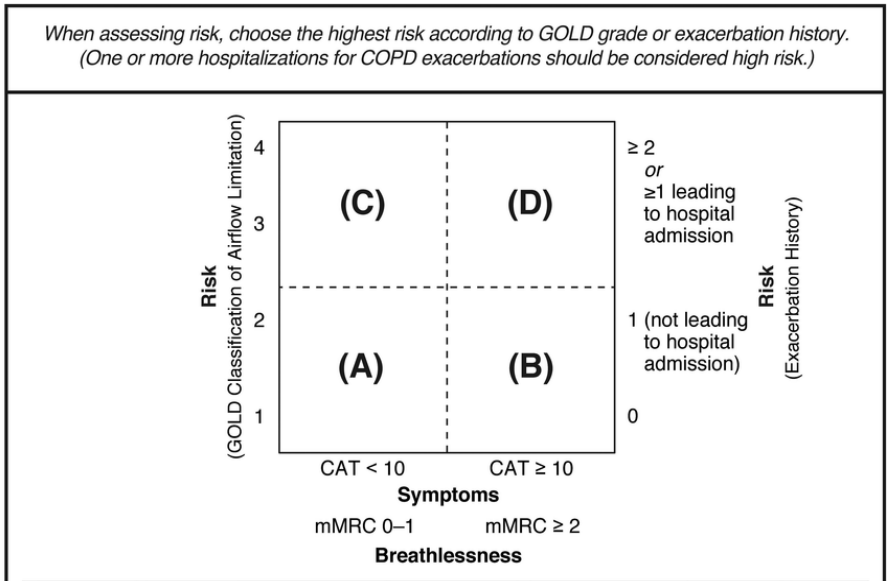
In the context of management in Primary Care, the SGRQ and other similar scoring systems are less appropriate due to their complexity and the consequent time taken to administer and interpret the result. The detail contained within them is more than required for the routine assessment of most stable COPD patients. Over the last ten years, several shorter assessment tools have been developed, aimed at more convenient clinical assessment of health status in those with COPD. The COPD Assessment Test (CAT) is one such tool (Appendix 1. The COPD Assessment Test [205]) [37]. Utilised by the GOLD guidelines in 2011 it has been included in each subsequent update as the recommended tool for quantification of symptom burden in COPD [8]. The CAT is an eight-item questionnaire, the eight questions focussing on dyspnoea, cough, chest

tightness, sputum production, sleep, energy levels, confidence and activities of daily living. Each question is scored on a scale of 0-5 giving a range of possible scores from 0-40, the higher the score, the greater the symptom burden.

CAT score has been demonstrated to be valid and reliable over several systematic reviews and to show good correlation with SGRQ and mMRC [38-40]. A consensus on minimal clinically important difference in score is yet to be established in the literature but studies thus far have suggested a range from 2 to 3.8 units [39]. A cut-off point of ≥10 in CAT score has been shown to identify an equivalent proportion of patients with a 'low symptom burden' from a COPD population to an mMRC score of ≥1, however, the composition of these two patient groups are different [27]. CAT score of ≥10 has been associated with increased exacerbation risk, depression and mortality when compared with an mMRC score of ≥1 [38].

The GOLD guidelines in 2014 recommended the introduction of a new assessment approach where spirometry values are combined with exacerbation number and symptom scores to divide patients into four groups [8]. These groups, A to D, represent either high or low risk, combined with, either a high or low symptom burden (Figure 1-3). The system uses a CAT score of ≥10 or an mMRC score of ≥2 to categorise the patient into a 'high symptoms' group despite their differences at systematic review and meta-analysis [38].

Figure 1-3 The GOLD Combined COPD Assessment [8]



Patient Category	Characteristics	Spirometric Classification	Exacerbations per Year	CAT	mMRC
A	Low Risk, Less Symptoms	GOLD 1–2	≤ 1	< 10	0–1
B	Low Risk, More Symptoms	GOLD 1–2	≤ 1	≥ 10	≥ 2
C	High Risk, Less Symptoms	GOLD 3–4	≥ 2	< 10	0–1
D	High Risk, More Symptoms	GOLD 3–4	≥ 2	≥ 10	≥ 2

The concept of combining assessments of physiology and symptom scores to stratify COPD is not a new one. The first multicomponent grading COPD index was developed in 2004 by Celli et al. The BODE index combined **B**ody-mass index (BMI), the degree of airflow **O**bstruction, mMRC **D**yspnoea score and **E**xercise capacity (6-minute walk test) to build a score from points allocated to each component (Figure 1-4). The index was demonstrated to predict mortality (all cause or respiratory specific) better than FEV_1 alone and was the first index to combine domains representing lung function, symptoms and the systemic consequences of the disease [41].

The BODE score has since been shown to be superior to the GOLD ABCD score in predicting mortality, exacerbation risk, hospitalisation, the presence of anxiety and depression and to be comparable to SGRQ in predicting quality of life [42-46]. BODE also responds to interventions such as lung volume reduction surgery and Pulmonary Rehabilitation [47-49].

Figure 1-4 The Body-Mass Index, Degree of Airflow Obstruction and Dyspnoea, and Exercise Capacity (BODE) Index [41]

Variables and Point Values Used for the Computation of the Body-Mass Index, Degree of Airflow Obstruction and Dyspnoea, and Exercise Capacity (BODE) Index				
Variable	**Points of BODE Index**			
	0	1	2	3
FEV_1 (%of predicted)	≥65	50-64	36–49	≤35
Distance walked in 6 min (m)	≥350	250-349	150-249	≤149
mMRC dyspnoea score	0-1	2	3	4
Body-mass index	>21	≤21		

Several modifications of the score have been investigated; iBODE and mBODE use an incremental shuttle walk or VO2 by progressive cycle ergometry respectively in place of the 6-minute walk test, eBODE combines the use of exacerbation rate into the index and BODEx replaces the 6-minute walk test with exacerbation rate. These modified indices have all been shown to have equivalent predictive mortality ability, but none has exceeded that of the original BODE score [50-52].

Whilst the BODE index is the most commonly used prognostic score in clinical practice, as with the SGRQ, its use is mainly limited to specialist respiratory settings. This is likely to be predominantly due to the inclusion of the 6-minute walk test, as the time required to perform the test often prohibits its use in Primary Care. With a view to addressing this, a Spanish research group (Puhan et al) developed the ADO index in 2009 (Figure 1-5) specifically for ease of use in a Primary Care [53]. The ADO index assigns points to **A**ge, mMRC **D**yspnoea score and airways **O**bstruction to build the score which has been demonstrated to predict severity and mortality [53-55]. The ADO

score is simple, swift to administer and well validated but provides little intrinsic guidance to how to subsequent patient management.

Figure 1-5 The Age, mMRC Dyspnoea score and airways Obstruction (ADO) Index [53]

Variable	Assignment of points of the ADO Index					
	0 points	1 point	2 points	3 points	4 points	5 points
FEV_1 (% predicted)	≥65%	≥36-64%	≤35%			
Dyspnoea (MRC scale)	0-1	2	3	4		
Age (years)	40-49	50-59	60-69	70-79	80-89	≥90

In 2009, the DOSE score was developed by Jones et al with the aim of providing a grading index that not only assessed health status in COPD but also helped to guide clinician management strategy [56]. The index is built in a similar way to the BODE and ADO scores with points being assigned to the components which measure **D**yspnoea, airways **O**bstruction, **S**moking status and **E**xacerbation rate (Figure 1-6). The resulting score ranges from zero to a maximum of eight with a score of ≥4 representing a 'high' DOSE index [56].

Figure 1-6 The DOSE Index, Dyspnoea, airways Obstruction, Smoking status and Exacerbation rate [56]

DOSE index points To build the DOSE Index score, the DOSE Index points associated with every category of all four variables are added up to maximum score of 8 points.				
	0	**1**	**2**	**3**
MRC Dyspnoea Scale Score	0-1	2	3	4
FEV_1 % predicted	>50	30-49	<30	
Smoking status	Non-smoker	Smoker		
Exacerbations per year	0-1	2-3	>3	

The DOSE index has been validated in several international cohorts and the authors demonstrated a high score to correlate with exercise capacity (highly correlated with the BODE Index and negatively correlated with 6-minute walk test and Body Mass Index). A high score was demonstrated to predict hospital admission, respiratory failure and exacerbations in the following year [56]. Subsequent research has demonstrated DOSE to be a better predictor of exacerbation than the BODE or ADO indices [57] and a high DOSE score to predict patients at greater risk of worsening health status than those with a low score [58]. A high DOSE score was shown to be significantly predictive of mortality but less so than the BODE or ADO index [50]. This finding was supported in 2013 when Sundh et al demonstrated a five-year mortality rate of 42.4% in those with a high DOSE score vs an 11.0% rate in those with a low DOSE score. They further refined this to show a hazard ratio for mortality of 3.48 in a score of 4-5 and a hazard ratio of 8.00 for a score of 6-7 when compared with a DOSE index score of 0-3 [59]. The combination of its risk predictive

properties and inherent guide to management has led to the DOSE Index being suggested as an appealing prospect for routine use in Primary Care [60].

1.4 The role of comorbid disease in COPD assessment

Over the last decade, increasing attention has been paid to the presence and impact of concurrent comorbidities in people with COPD. A personal history of tobacco smoking, low physical activity levels and corticosteroid treatment are just some of the factors that predispose those with COPD to increased comorbidity prevalence. Investigation into the links between comorbidity and COPD can be challenging as, given the causation and physiological effect of COPD and its treatments, comorbid disease entities tend to fall into two groups:

i. Disease processes such as ischaemic heart disease or cancer which share a common pathological factor (tobacco smoking) with COPD
ii. Diseases which are a known consequence of the pathological effects of COPD or its treatments e.g. Cor pulmonale in severe COPD or the development of diabetes mellitus and osteoporosis following oral corticosteroid use.

1.4.1 Systemic inflammation in COPD

Research is ongoing into the role played by systemic inflammation, and its link to the prevalence of other co-morbidities and mortality in COPD. Persistent low grade inflammation is a known risk factor for the presence of cardiovascular disease, cachexia and cancer [3] and it is postulated that this may be a common physiological pathway contributing to the lung parenchymal destruction seen in COPD [61, 62]. Inflammatory mediators such as C-reactive protein, interleukin-6, interleukin-8, and fibrinogen from the inflamed airways may migrate into the circulation and act on other organs, expediting disease pathologies such as atherosclerotic plaque formation in ischaemic heart disease [3].

Various substances have been investigated as potential biomarkers of systemic inflammation. Within blood markers, high fibrinogen levels have been associated with COPD progression, increased exacerbation rates, lower FEV1 % predicted and increased respiratory symptom burden [63]. Haemoglobin level, lymphocyte number and haematocrit have been demonstrated to be related to all-cause mortality in those with very severe COPD [64]. Anaemia has also been suggested to be associated with increased morbidity, mortality and decreased exercise tolerance [65]. Poorer health status has been demonstrated in those with increased macrophage levels in

induced sputum [66] and the presence of pseudomonas in the sputum post hospital admission has also been linked to mortality [67]. Interleukin 6 levels have been shown to improve the predictive ability of a mortality model in COPD and this was improved further by the addition of a panel of eight other biomarkers [68].

Eosinophilia is present in a subset of patients and, when present, this may be a modifiable disease element which could be used to monitor disease activity [69, 70]. Blood eosinophilia has been linked to increased mortality in COPD [71] and Siva et al demonstrated a reduction in severe exacerbation frequency in those with treated high sputum eosinophil counts (>3%) when the steroid route and dose was titrated to eosinophil count [69]. Negewo et al demonstrated that peripheral blood eosinophil count is highly correlated to sputum eosinophilia and can be used in situations where sputum analysis is impractical [72].

Overall the relationship between a multitude of biomarkers for systemic inflammation and the presence of COPD is fairly established, as is the suggestion that this may provide a common pathway to some co-morbid conditions. At present there is no clear consensus on the relationship between systemic inflammation and mortality in COPD and more work is needed to further develop the practical use of biomarkers as a measure of disease activity across all COPD phenotypes.

1.4.2 Cardiovascular Disease

Cardiovascular disease has been demonstrated to have higher prevalence in those with COPD than in the general population [73]. It is the commonest co-morbidity associated with very severe airways obstruction in COPD, (strongly associated are hypertension followed by ischaemic heart disease, arrhythmias and congestive cardiac failure) [35]. Hypertension, ischaemic heart disease (both clinical and sub clinical), heart failure, atrial fibrillation and peripheral vascular disease have all been shown to increase in prevalence as airways obstruction becomes more severe [73, 74]. Conversely, cardiovascular disease and cancer are the commonest cause of death in mild to moderate COPD whilst respiratory failure is responsible for the majority of deaths in those with more severe airways obstruction [61].

That cardiovascular disease, particularly those disease entities driven by atherosclerotic plaque formation (i.e. ischaemic heart disease and peripheral vascular disease) are more prevalent in those with COPD is unsurprising given they share the common pathological process of tobacco smoking. The relationship is more complex than this however as other factors such as tissue hypoxia and high pulmonary pressures secondary to lung parenchymal destruction will also play a

role. This is borne out by studies demonstrating coronary artery calcification (pathognomonic of coronary artery disease) is significantly greater in those with COPD, not just compared to non-smokers but also when compared to smokers with normal spirometry [75].

Studies have found that those with cardiovascular disease have double the risk of COPD-related hospitalisation, higher BODE score, poorer quality of life and higher symptom burden measures than those without cardiovascular disease [63, 76]. Both the presence of chronic and acute cardiac disease during exacerbations requiring a hospital admission have been demonstrated to predict increased mortality post discharge [77, 78].

Further muddying the waters in the relationship between COPD and cardiovascular disease is the impact of COPD on disease severity and trajectory in cardiovascular disease. COPD has been associated with poor outcomes post myocardial infarction and poorer survival in those with heart failure [79, 80].

COPD patients with left ventricular failure have been shown to have some of the highest mortality rates amongst the COPD population [64, 81]. The diagnosis poses a particular challenge as the symptoms can be difficult to distinguish from that of COPD. One study found left ventricular dysfunction present in 32% of COPD patients presenting with a symptomatic deterioration, however physicians' clinical evaluation struggled to distinguish these patients from those in whom symptoms related purely to COPD [82]. The under diagnosis of these cardiovascular co-morbidities may partially explain increasing evidence that the use of beta-blockers appears to improve mortality rates in COPD, independent of the presence of diagnosed cardiac disease [83, 84].

1.4.3 Mental health disease

Most patients with COPD will experience some low mood symptoms during periods of poor health and exacerbation but even allowing for these transient symptoms, levels of depression are higher in those patients with COPD than in the general population, estimated in some studies to be as high as 60% [85]. The association between depression and COPD is stronger than that of other chronic illnesses including, coronary artery disease, stroke disease, diabetes mellitus, arthritis and cancer [86].The prevalence rises with disease severity [87]and in those living alone [86].

Co-existent depression in those with COPD has been associated with higher mortality [88, 89], to increase rates of exacerbation, increase risk of hospitalisation and increase rates of readmission post-hospital discharge [46, 89-93]. There are many studies demonstrating that those with co-

existent disease have poorer functional abilities and poorer quality of life measures than those with COPD without depression [88, 94-96].

A recent study amongst Swiss patients suggested an association between lower FEV_1 values and the presence of other co-morbidities in those with depressive symptoms but also highlighted that the Hospital Anxiety and Depression scale (a common tool used to screen for depressive symptoms), has low diagnostic accuracy in those with COPD which may reduce diagnosis rates [97]. It has been estimated that up to 25% of patients with COPD may have undiagnosed depression and only a third of those with co-existent disease are likely to receive treatment with antidepressants [3, 98]. It remains unclear whether treatment of depression in COPD can reduce its poor prognostic effects.

Anxiety is more common in patients with COPD than in the general population and in those with other chronic illnesses, with one study estimating its prevalence to be as high as 19% [3]. The relationship between anxiety and frightening breathlessness is not unexpected, but is independent of severity of airways obstruction and confers one of the biggest risks to patients with COPD in terms of mortality rates, hospitalisation and readmission risk [92, 99]. Those with anxiety are also more likely to hospitalised earlier in their disease course. Independent of depression, anxiety is associated with poorer measures of quality of life, functional ability and increased breathlessness [100, 101].

Those with mental health problems are more likely to have smoked and more likely to continue to do so [98]. As tobacco smoking is key to symptom control and lowered mortality in COPD, one might expect poorer outcomes in those with mental health problems, however the relationship appears to be more complex than this [102]. Poorer mental health may also impair patients' ability to recognise symptoms and consequently self-manage their disease [101, 103], as well as to engage in pulmonary rehabilitation, the two strategies most heavily emphasised in COPD treatment across both Primary and Secondary Care services.

1.4.4 Gastro-oesophageal reflux disease (GORD)

Gastro-oesophageal reflux disease occurs, when the acidic contents of the stomach, in either liquid or gaseous form, refluxes up through the oesophagus and into the mouth. The association between GORD and significant lung damage is well described in the literature and is thought to be caused by tiny amounts of the acidic stomach contents being inhaled into the lungs [104]. The causal relationship between GORD and COPD is further complicated by the effect of oral prednisolone on the stomach lining, which can cause irritation of the gastric mucosa and

increased gastric acid production. Coughing also increases intra-abdominal pressure making the stomach contents more likely to reflux into the mouth and consequently the lungs, further destroying already damaged lung tissue [105].

The presence of GORD is known to negatively affect asthma control [104] and there is some evidence of it being associated with increased exacerbation rates in COPD [106, 107]. There is a suggestion in the literature that there may be an increased prevalence of asymptomatic GORD amongst those with COPD [108] and some studies have suggested it may be the second strongest predictor of exacerbations, with only a previous history of exacerbation being more strongly associated [3]. As one might expect, GORD appears to be more closely associated with more severe airways disease [35] and has been demonstrated to increase symptom burden [105]. Treating GORD in COPD with a proton pump inhibitor has not been conclusively shown to improve exacerbation rates [109], perhaps because the right patient subset has not yet been targeted.

1.4.5 Diabetes Mellitus

Those with COPD have a higher incidence of developing diabetes mellitus than the general population, with a prevalence varying from 10.3% to 18.7 % [110-114]. In addition, those with diagnosed diabetes mellitus are at increased risk of developing COPD [115]. The presence of diabetes in COPD has been shown to increase hospitalisation risk, the time to first hospitalisation, hospital admission mortality risk and overall mortality [110]. Co-existent diabetes mellitus is also associated with poorer markers of functional ability and symptomatic control [110, 112, 116].

Metabolic syndrome is the combination of disordered blood glucose, high blood lipids, hypertension and central obesity. It predisposes patients to cardiac comorbidity and the development of diabetes [117, 118]. Studies have shown links between central adiposity and poorer lung function tests in those with COPD and this relationship is stronger in current and ex-smokers [117, 118].

The mechanism proposed to be common to the development of diabetes, metabolic syndrome and COPD, is that of systemic inflammation, with increased circulating levels of pro-inflammatory enzymes and cytokines resulting in increased insulin resistance [117, 118]. High levels of oral corticosteroid use, and even high levels of inhaled steroid have been demonstrated to promote central adiposity, insulin production and insulin resistance as well as contributing to poor diabetic control [65, 118]. Tobacco smoking increased the risk of developing diabetes two-fold compared to that of non-smokers [119, 120].

1.4.6 Malnutrition and cachexia in COPD

In those with COPD, malnutrition and cachexia become more common as severity increases. This is felt to be due to the energy required for increased work of breathing and sustained systemic inflammation causing significant catabolism. This catabolic state leads to fat and muscle breakdown and consequent muscle weakness, this process is clinically manifested as weight loss [121]. Low BMI is an accepted risk factor of poor prognosis within the clinical and research field [63, 122, 123]. Evidence exists linking it to impaired pulmonary function, reduced diaphragmatic mass, decreased exercise capacity and increased mortality when compared to a normal BMI [122]. High fat free mass and malnutrition status have also both been shown to predict mortality in those with COPD [54, 81].

Evidence is starting to accrue to suggest better outcomes in those with COPD with a BMI in the overweight and obese categories compared to those with a BMI considered normal in those with COPD [20-25, [124]]. Currently, the relationship between these studies and weight loss are unclear. The possibility exists that some of the risk associated with a 'normal' BMI group may in fact represent those who started in a higher BMI category and who have already entered the negative cycle of catabolism and weight loss.

Encouragingly, evidence also exists that much of this risk is reversible with increasing nutritional intake. Nutritional supplementation has been demonstrated to increase weight, increase respiratory muscle strength and reduce symptom burden [122]. Currently, the optimal point of intervention, and exact form that supplementation should take, is unclear [8].

1.4.7 Cognitive Impairment

The relationship between cognitive impairment and COPD is not yet clear but is clinically very important. It is often challenging to involve those with cognitive impairment in research and this may be why they are unrepresented in the research literature.

COPD has been identified as a significant risk factor for cognitive impairment, particularly in those with significant hypoxaemia [125]. Drawing impairment (as a measure of cognitive impairment) in hypoxaemia has been shown to increase mortality risk [126] and it has also has been demonstrated that cognitive abilities worsen during exacerbation compared to stable state COPD [127].

The link between cognitive impairment and COPD is likely to be multifactorial and include hypoxaemia, comorbid cardiovascular disease and lack of physical activity [125, 128, 129]. Key to current COPD management strategies is the patient's ability to recognise the signs and symptoms of deterioration early and then utilise self-management strategies. Most of the resource available for patients with COPD, (a personalised self-management plan, education programs and breathing control techniques) focus on this strategy. For those with concurrent cognitive impairment this may be very difficult or even impossible. In the very mild stages of cognitive impairment, or for those with predominantly frontal lobe impairment, their ability to manage the practical aspects of their life may appear normal, but the higher functioning abilities required to self-manage can be significantly impaired [130-132]. This can be further exacerbated by the worsening of cognitive function that occurs during illness, and hypoxia that occurs during an exacerbation, just at the point it is most important patients are able to self-manage. This group of patients are at a significant disadvantage and rely on this being identified. They may need modified management strategies, promoting the involvement of family members or carers, rather than the current self-management structure of COPD.

1.4.8 Asthma

Asthma is caused by airways narrowing and produces symptoms of wheeze and dyspnoea, not dissimilar to COPD. Unlike COPD, the airway narrowing seen in asthma is caused by a temporary reaction to an allergen or airway irritant rather than by tobacco smoking. Key differences between the two are that the airways narrowing in asthma is reversible rather than fixed and those with asthma do not develop the lung parenchymal damage seen in emphysema.

Whilst COPD and asthma are two separate clinical entities, the relationship between the two is complex. Over time, people with asthma may develop irreversible airways narrowing or those with asthma may have smoked, giving rise to both disease entities. As the symptom and treatment of asthma and COPD are similar, distinguishing the diagnoses is complex and may not always be possible. A missing diagnosis may lead to suboptimal treatment of either of the two disease entities [8].

Physician diagnosed asthma is a predictor of frequent exacerbations in COPD [133] and there has been increasing suggestion that a distinct 'frequent exacerbation phenotype' exists within the COPD population although this has more application as a research concept than a recognised clinical entity at present [23]. The concept of the 'Asthma-COPD overlap syndrome' (ACOS) for patients with clinical features of both asthma and COPD has been increasingly recognised as a

clinical diagnosis over the last ten years. The findings of a joint project between the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) were published in 2015 with the joint aim of providing guidance for clinicians on diagnosis and management and to stimulate further research into the overlap syndrome [134].

1.4.9 Concurrent lung disease

Bronchiectasis has a high prevalence of in COPD and some evidence appears to suggest it confers an increased risk of mortality [135, 136]. Whilst it is seen fairly frequently as an incidental finding on Computer Tomography (CT) scan, as a result of traction due to lung parenchymal damage, these patients may not behave in a typically bronchiectatic fashion and clear guidance does not exist as to how the combination of diseases should be managed [137].

Concurrent COPD and Pulmonary Fibrosis has been seen in up to 8% in study populations [138]. It appears to take two forms, either following established radiological patterns recognisable as those seen in Idiopathic Pulmonary Fibrosis (IPF), or, in a different distribution which has been recognised as separate clinical entity 'Combined Pulmonary Fibrosis and Emphysema' (CPFE). In CPFE, fibrosis and associated traction bronchiectasis are seen predominantly in the lower lung lobes with bullous emphysema seen in the upper lobes [3, 114, 139]. Patients with CPFE, have a higher mortality, faster disease progression and an increased incidence and severity of pulmonary hypertension and lung cancer than those with COPD alone. No treatments have been shown to improve current median survival rates of six years [140-144]. The combination of lung pathologies also leads to pulmonary function tests which are not typical of either disease process, potentially delaying diagnosis and causing a lack of recognition from health professionals regarding disease severity and the rate of disease deterioration [141, 142].

An episode of pneumonia in a patient with known COPD has consequences distinct from that of an infective exacerbation of COPD without pneumonic changes. That the two cannot be effectively distinguished without access to a chest radiograph makes estimating the true disease burden a challenge. Community acquired pneumonia is commoner in those with COPD than in the general adult population [145] and in a UK national audit of COPD related admissions, 18% of patients were found to have pneumonic changes on admission chest radiograph [146]. Hospitalisation with a community acquired pneumonia in COPD carries a worse prognosis compared to an admission related to a non-pneumonic exacerbation [147, 148]. This may be partly due to the underlying frailty of the patient group hospitalised with pneumonia with one

study demonstrating these patients to be older with greater severity of their underlying COPD [149].

1.4.10 Osteoporosis

The combination of decreased activity levels, poor nutrition, a history of tobacco smoking and corticosteroid use puts COPD patients at increased risk of osteoporosis. It is likely that systemic inflammation contributes by increasing bone turnover rate as does vitamin D deficiency which is also seen in high prevalence within the COPD population [61, 150]. The prevalence of osteoporosis in COPD patients is estimated to be as high as 69% in some studies and is raised in both female and male patients [151].

The clinical effect of osteoporosis is of significant concern in those with COPD. Osteoporotic vertebral and rib fractures cause significant pain and kyphosis which can limit both the mechanics of breathing and general mobility [3]. This leads to poorer sputum clearance and lower activity levels, both well-established risk factors for poorer quality of life and increased mortality risk [8]. Vertebral fractures have been associated with increasing age, long term oxygen therapy, lower FEV_1 percentage predicted and corticosteroid or warfarin treatment [152]. Asymptomatic vertebral fractures have also been linked to accelerated lung function decline [150]. The presence of osteoporosis in COPD has been associated with female gender, increased dyspnoea, decreased functional ability, lower BMI, more severe airway obstruction and long term oxygen therapy [152, 153].

1.4.11 Sleep disorders

Disturbed sleep in COPD has been shown to be associated with cough, dyspnoea and increased COPD severity score [154]. It has also been shown to predict exacerbation rate, hospitalisation, poorer general and respiratory quality of life scores and to be associated with higher mortality rates [154, 155]. The most well-known sleep related breathing disorder is Obstructive Sleep Apnoea (OSA). OSA was found to have a prevalence of 20% in one outpatients study and was predicted by BMI and pack year history in multivariate analysis. As would be expected, higher concurrent rates of diabetes mellitus and hypertension were seen in the cohort with both COPD and OSA [156].

1.4.12 Lung cancer

Lung cancer is more prevalent in smokers who have developed COPD than in those smokers without COPD [157, 158] and even more so in those who have developed emphysema [159]. Lung cancer and cardiovascular disease account for two thirds of the deaths in those with mild and moderate COPD with the common pathological process behind this postulated to be the presence of systemic inflammation [61, 137]. Whilst the treatment of lung cancer should not differ in those with and without COPD, the additional co-morbidity and structural lung abnormality COPD confers often makes patients less suitable for surgical and chemotherapeutic treatment options. This should be less so in the case of mild COPD but as the early warning signs of lung cancer such as cough and dyspnoea are common to COPD, they may be initially attributed to the patient's COPD diagnosis, potentially delaying the identification of lung cancer and leading to less favourable outcomes. Several large studies have shown the potential of CT screening of patients with COPD to reduce death rates from lung cancer [160, 161]; however research is ongoing into how this can be provided in a clinically efficient and cost effective manner [162].

1.5 Composite comorbidity scoring indices in COPD

As discussed in section 1.3, the main tools used to prognosticate in COPD have been the GOLD staging scores of airways obstruction and multidimensional indices such as the BODE and DOSE Index. The 2014 GOLD guidelines recognised, within international guidelines, the growing body of evidence supporting COPD as a multisystem disease with distinct phenotypes and advocated the importance of diagnosing and treating concurrent co-morbidities [8].

Given the wealth of evidence around the effect of individual co-morbidities the next logical step is to utilise them into composite scoring systems designed to better identify and manage those at risk of poorer prognosis in COPD. The concept of using comorbid disease to assess mortality risk is well established in the medical community with the best known comorbidity score beings the Charlson Comorbidity Index [163]. Developed in 1987 for use in longitudinal research studies, it uses the presence of seventeen different co-morbidities, each individually weighted, to predict mortality. The Index has been updated over the last thirty years to reflect changes in individual disease mortality, the most striking example of this is being the reduction in the weighting of HIV with the introduction of effective antiretroviral treatment [164]. It has also been adapted to work with the update of the International Classification of Disease-Version 10 [165].The components of the Index are shown in Figure 1-7 The Charlson Comorbidity Index [164] which demonstrates the

form the index is currently used in the NHS based Dr Foster data where it is used to represent the role comorbid disease is expected to play in hospital mortality rates in the UK [164].

Figure 1-7 The Charlson Comorbidity Index [164]

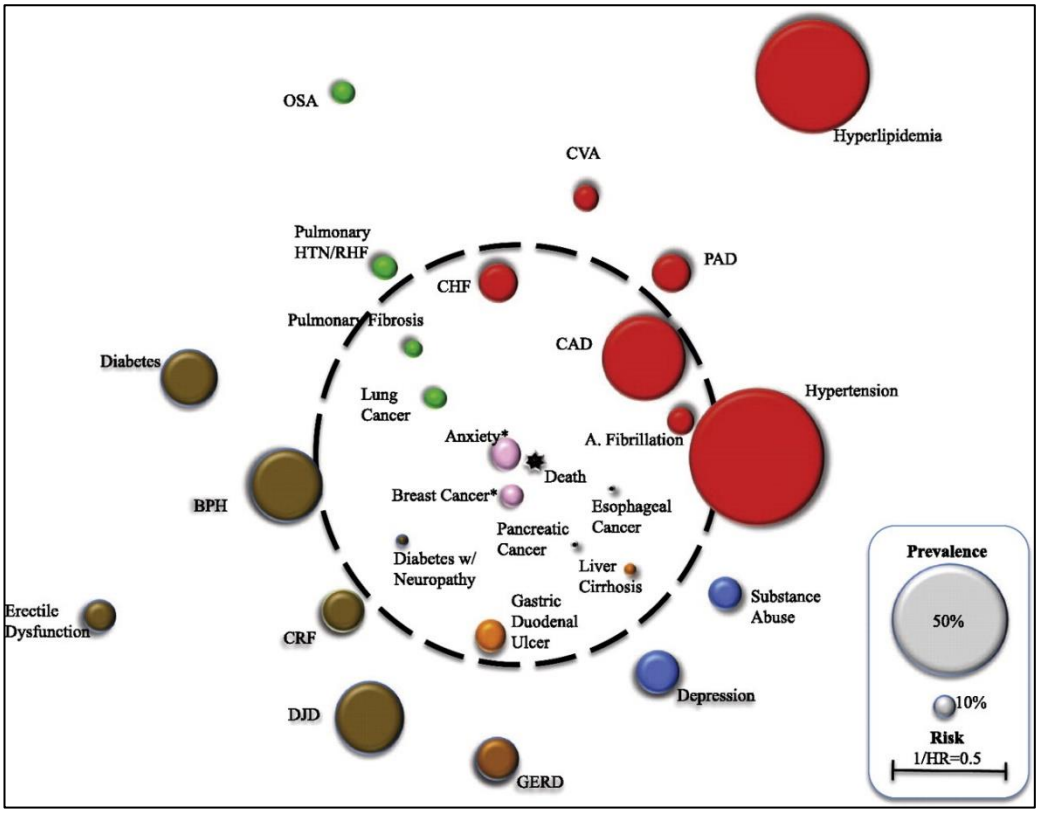
Condition number	Condition name	Weighting
1	Acute myocardial infarction	5
2	Cerebral vascular accident	11
3	Congestive heart failure	13
4	Connective tissue disorder	4
5	Dementia	14
6	Diabetes	3
7	Liver disease	8
8	Peptic ulcer	9
9	Peripheral vascular disease	6
10	Pulmonary disease	4
11	Cancer	8
12	Diabetes complications	1
13	Paraplegia	1
14	Renal disease	10
15	Metastatic cancer	14
16	Severe liver disease	18
17	HIV	2

The Charleston Comorbidity Index has been investigated for its utility in COPD mortality risk calculation and was shown to have some predictive properties regarding inpatient treatment and inpatient exacerbation mortality (22, 47, 84-86). However, when used in the context of stable COPD it performs less well [81, 166], perhaps reflecting the comorbidity disease distribution peculiar to the COPD population.

In 2012 the CO-morbidity TEst (COTE Index) was published by the research group responsible for the development of the BODE Index [167]. The patient cohort used to develop the BODE index totalled 1664 patients recruited within the USA and Spain between 1997 and 2009, reviewed annually and followed until death or March 2010. Comorbidities had been systematically recorded for the cohort and using multivariate analyses and regression techniques the group developed a "Comorbidome" (Figure 1-8) portraying the relationship between comorbidity prevalence and mortality.

Figure 1-8 The COTE Comorbidome [167]

Reproduced from the original paper, the Comorbidome is a graphic representation of the study findings. The area within the circle represents the comorbidity prevalence and the distance from the centre of the circle represents the strength of the association between the comorbidity and the risk of death (the closer to the middle, the stronger the association. All abbreviations are written in full in the abbreviations section.



The COTE index (Figure 1-8) was created using similar methods to the Charlson Comorbidity Index, with the intention of making the research more accessible to those at the point of care. It uses a points system to weight the presence of those comorbidities with a statistically significant hazard of death [167].

Table 1-2- The COTE Index [167]

Comorbidities and point values used for the computation of the COTE Index. A hazard ratio of 1-1.5=1 point, 1.5-2= 2 points, 2 or more =6 points. The exception to this is 'other cancers' which was assigned two points. *breast cancer and anxiety are valid on the female population only.

Comorbidity	Hazard Ratio	Point Assignment
Lung, oesophageal, pancreatic and breast* cancer	>2.00	6
Anxiety*	13.76	6
All other cancers		2
Liver cirrhosis	1.68	2
Atrial fibrillation/flutter	1.56	2
Diabetes with neuropathy	1.54	2
Pulmonary Fibrosis	1.51	2
Congestive heart failure	1.33	1
Gastric/duodenal ulcers	1.32	1
Coronary artery disease	1.28	1

The COTE Index confers a hazard ratio for death of 1.14 per point for COPD patients followed for eighteen months or more (COPD specific and all-cause mortality). A score of four or more was statistically significant in conferring a 2.3-fold increased risk of death. BODE index was (as expected) a significant predictor of death but the combination of the COTE and BODE index was also statistically significant when predicting death with a COTE index of four or more conferring a 2.2-fold increased risk of death for each BODE quartile (BMI, Airways Obstruction Dyspnoea, Exacerbation rate) [167]. The COTE index has been validated and shown to have either similar or greater predictive properties to the Charlson Comorbidity Index and GOLD ABCD score in predicting mortality in very severe COPD and in those attending outpatient clinics, a relationship that is even stronger when combined with age [45, 54].

Published in 2014, the COMCOLD research group set out to develop a composite comorbidity index of the effect of comorbidity on health status rather than mortality [168]. The study used patients from the International Collaborative Effort on Chronic Obstructive Lung Disease: Exacerbation Risk Index Cohorts (ICE COLD ERIC), recruited from Primary Care in Switzerland and the Netherlands with patients excluded if they were felt to have a life expectancy of less than twelve months. Comorbidities were self-reported or taken from medical records and the Hospital Anxiety and Depression Score was used to assess for anxiety and depression. Of note, asthma was not considered as comorbidity as the symptoms were felt to be too similar to that of COPD. The primary outcome recorded for patient health status was the 'feeling thermometer' the modified visual analogue scale of EuroQol's validated EQ-5D measure of quality of life.

In decreasing order, depression, anxiety, peripheral arterial disease, cerebrovascular disease and symptomatic heart disease (ischaemic heart disease/heart failure) were found to be the most significantly associated with poorer patient reported health status. The '**COM**orbidities in **C**hronic **O**bstructive **L**ung **D**isease', COMCOLD index (Table 1-3) was developed using a regression analysis and as is built as the COTE and Charlson Comorbidity Indices, with comorbidity weighting reflected by the number of points attributed to the individual disease. The score ranges between 0 (no impact of comorbidity on health status) to 19 (very large impact on health status). The index showed no correlation with disease severity as measured by FEV_1 percentage predicted [168].

Table 1-3 The COMCOLD Index [168]

Comorbidity	Points
Depression	6
Anxiety	4
Peripheral Vascular Disease	3
Cerebrovascular disease*	3
Symptomatic heart disease**	3

**Cerebrovascular accident or transient ischaemic attack*

*** Coronary heart disease and/or heart failure*

Later in 2014, Putcha et al sought to develop an Index reflecting comorbidity burden on outcomes of respiratory specific quality of life measured by the SGRQ and 6-minute walk distance [169]. Using the COPDGene (Genetic Epidemiology of COPD) cohort data, a multicentre observational study of approximately 10,000 current and former smokers in the United States, the group investigated the advantages of weighted scoring methods over a simple comorbidity count using fourteen different comorbid diseases (Table 1-4) and found them to be comparable [170]. The comorbidity count was validated in SPIROMICS (Subpopulations intermediate outcome measures in COPD study), a multicentre observational study, based in the United States, aiming to identify subgroups of COPD patients with similar baseline characteristics to participate in research studies [171]. The cohort was divided into those with two or less comorbidities and those with three of more comorbidities. The higher comorbidity count was found to be significantly associated with a higher St George's Respiratory Questionnaire score, mMRC score, 6-minute walk distance and risk of exacerbation [169]. A strength of the comorbidity count is its simplicity and the deliberate selection of specific comorbidities rather than broad categories such as 'cancer' which can be difficult to quantify given the range of conditions that can encompass. The negative effect of such a simplistic score are that requiring only three of very common co-morbidities required to place a patient in the 'high' category would place a large number of patients into the high risk category. This may make it less attractive for use in day to day practice, particularly as it is not clear from the score which co-morbidities should be most strongly targeted in any subsequent management plan.

Table 1-4 The comorbidities used to make up the Comorbidity Count and their weightings in the weighted score [169]

Comorbidity	Weighting
Coronary heart disease	4.93
Diabetes	4.69
Congestive Heart Failure	6.53
Stroke disease	5.96
Osteoarthritis	5.13
Osteoporosis	4.31
Hypertension	3.24
High cholesterol	2.14
Gastro oesophageal reflux disease	6.45
Stomach ulcers	4.94
Obesity	5.00
Obstructive Sleep Apnoea	8.83
Hay fever	2.75
Peripheral vascular disease	3.71

1.6 Data recording within the NHS

With data increasingly stored in electronic format in both Primary and Secondary Care, a need was recognised for a unifying method of recording information to allow data extraction for searches, audit, analysis and interpretation of the data complied. Without this, extraction of data from free text becomes overwhelmingly complex and the potential for inconsistency in any sort of data analysis becomes unacceptably high. Various coding systems exist where clinical terms are assigned a numerical code and use of these systems makes possible comparable and consistent data extraction within and between different healthcare settings and locations.

1.6.1 International Classification of Diseases

The International Classification of Diseases (ICD) is an internationally accepted classification system of disease entities, symptoms and other factors with over eight thousand corresponding alphanumerical codes. It has been developed and maintained by the World Health Organization with the principal aim to facilitate international morbidity and mortality data recording. The ICD is regularly updated and the current version, in use since 1994, is version 10 (ICD-10), with version 11 released in June 2018 to enable the preparation needed for its implementation [172]. The alphanumerical codes in the ICD-10 range from A00-Z99. A fourth numerical code can be added after a decimal point if more detail is required from the clinical term [173]. The ICD-10 codes are the system used to facilitate the calculation of Hospital Standardised Mortality Ratios, the measure against which hospital inpatient mortality performance is judged in the UK [164].

Consequently, the ICD-10 is the data coding system currently in use in Secondary Care to record the details of all inpatient and outpatient activity.

1.6.2 Read codes

Extraction of electronic data records within Primary Care in the NHS is based around a system of Read Codes, numerically coded versions of clinical terms. Individual Primary Care Practices may use different data management systems and software interfaces to manage patient records but common to all practices are the use of Read Codes allowing clinicians to record clinical diagnoses, symptoms, investigations and management plans in a consistent manner. These codes were developed by (and named after) Dr James Read in the 1980s and have been in use in the NHS since 1985 [174]. In 1988 a joint statement by the Royal College of General Practitioners and the British Medical Association recommended their use nationally [175]. The use of Read codes is now embedded in day to day practice and the presence of a universal coding scheme has been essential for Primary Care strategy developments such as 'The Quality Outcomes and Framework' (QOF), the system by which Primary Care Practices are financially rewarded for chronic disease management [175].

There are over one hundred and twenty thousand different Read Codes stored in the 'Technology Reference data Update Distribution site', TRUD [176]. Version 2 of the TRUD Read Code system assigns a five character alphanumeric code to each clinical term. The Read codes are arranged in a hierarchical manner within the database allowing the user to select an increased level of clinical detail as they move down the hierarchical system [173].

1.6.3 The Quality Outcomes and Framework (QOF)

The Quality Outcomes and Framework (QOF) is the scheme by which implementation of national recommendations for chronic disease management, public health measures and preventative strategies are measured and financially rewarded in Primary Care [177]. Each year the National Institute for Clinical Excellence, NICE, publishes a series of clinical recommendations for most prevalent chronic conditions and those public health measures most felt to benefit from national consistency in care and felt to be potentially appropriate for inclusion in the QOF [178]. The final decision as to which indicators are included in each year's QOF rests with the UK Department of Health and NHS England [178]. Each clinical recommendation is taken as an outcome measure and individual Primary Care Practices must submit data proving they have achieved the outcomes over a set percentage of their patients to qualify for a financial reward [177].

Participation in the QOF scheme is voluntary but the vast majority of Primary Care Practices take part with almost 7,800 Practices participating in 2014/2015. The results are published annually, in both publicly available documents and online, detailing individual practice results as well as describing national trends [179]. Patients can be formally recorded as exceptions to a QOF indicator either for a clinical reason or due to the patient's personal preference and Read codes exist to document this exception status.

In 2014/2015 there were nineteen chronic conditions included in the QOF recommendations, one of which was COPD. Practices are required to keep a disease register of those patients with COPD. The six clinical indicators set out for those on the COPD register are detailed below [179]:

- The practice establishes and maintains a disease register.
- The percentage of patients with COPD (diagnosed on or after 1 April 2011) in whom the diagnosis has been confirmed by post bronchodilator spirometry between 3 months before and 12 months after entering on to the register.
- The percentage of patients with COPD who have had a review, undertaken by a healthcare professional, including an assessment of breathlessness using the Medical Research Council dyspnoea scale in the preceding 12 months.
- The percentage of patients with COPD with a record of FEV1 in the preceding 12 months.
- The percentage of patients with COPD and Medical Research Council dyspnoea grade of 3 at any time in the preceding 12 months, with a record of oxygen saturation value within the preceding 12 months.
- The percentage of patients with COPD who have had influenza immunisation in the preceding 1 August to 31 March.

The results are published as both a percentage of patients in whom an outcome has been recorded for each clinical indicator, the proportion of patients in whom the outcome has been achieved and the percentage of patients reported as exception to the indicator. Overall disease prevalence rates for each practice are also published [179]. The QOF recommendations have embedded the measurement of the MRC breathlessness score and spirometry use in Primary Care Practice but do not reward Practices for implementation of any management measures.

1.7 Moving forward in COPD management.

1.7.1 Clinical perceptions of COPD

The concept of smoking related lung damage is believed to have been first described by Theophile Bonnet in 1679 following his finding of cadaveric 'voluminous lungs' [180] and the term 'Chronic Obstructive Pulmonary Disease' was first used in 1965 at the 9th Aspen Emphysema Conference [180]. Despite this widespread and longstanding awareness of the disease and its significant morbidity and mortality impact, COPD has lagged behind other leading causes of smoking related mortality such as cardiovascular disease and cancer in health resource allocation and public interest and understanding [5].

The link between poverty and COPD is strong and this may account for some of the lack of historical prioritisation of the disease entity. Approximately 90% of deaths from COPD occur in low- and middle-income countries globally [2] and it has been robustly demonstrated that within developing countries, significantly higher COPD prevalence rates are seen in the lower socioeconomic groups [1]. This relationship between poverty and COPD is likely to be multifactorial in nature and amongst others, reflect factors including healthcare access and utilisation, nutritional status, education levels and extent of exposure to airborne pollutants [1, 181].

Another factor contributing to the low historical profile of COPD has been a lack of motivation and interest from the medical community in diagnosing and managing the disease. Significant nihilism has existed around the disease with a feeling that, with the possible exception of smoking cessation, there were no management options available to alter an inevitable progression in disease course. Significant historical resistance has occurred to the suggestion of proactive diagnosis early in the disease course, with Physicians expressing the opinion it was not in patients' best interest to make an early diagnosis with no useful treatment options. This has added the lack of public awareness of the disease and likely contributed to the significant underreporting of true disease prevalence rates [181, 182]. The developments in management strategies and therapeutic options over the last fifteen years including long acting bronchodilators, more accessible inhaler devices, Pulmonary Rehabilitation and lung volume reduction techniques have gone some way to altering this perception but significant work is still required to ensure all symptomatic COPD patients are diagnosed and optimally managed in a timely manner [1, 182].

1.7.2 Integration of Primary and Secondary Care and specialist review in long term COPD management.

The vast majority of patients with COPD will be managed exclusively in Primary Care with only a small subset of patients meeting a member of a respiratory specialist MDT [183]. In 2008, the British Thoracic Society released a "Statement on criteria for specialist referral, admission, discharge and follow-up for adults with respiratory disease" [183] this was aimed primarily at who and when to refer into secondary care for either acute or chronic management review but the statement also encouraged collaboration and integration of different services to improve quality and continuity of care. In a 2013 Cochrane review of models of integrated care for patients with COPD, mixed result were seen, but overall patients improved in quality of life scores and walking distance and had a decreased number of shorter hospitalisations [184]. A King's Fund report in 2014 suggested that as Primary Care teams are asked to manage increasingly complex respiratory patients a skills gap may exist. Specialists working within Primary Care teams provide an opportunity to fill this gap with education, training and advice, improving patient diagnosis and care [185].

Metting et al, reported a spirometry and questionnaire-based assessment and advice service provided by Respiratory Specialists in the Netherlands for Primary Care COPD and asthma patients showed improved disease control scores [186]. Gillet, Lippiett, Astles et al reported that high risk asthma and COPD patients proactively identified and reviewed in a joint primary and secondary care clinic showed reduced β agonist use, unscheduled GP visits and exacerbations over the subsequent nine months [187].

1.7.3 The development of risk stratification scores.

The outcomes and health related quality of life in those with COPD remain poor even in comparison to those with other chronic diseases. Nationally, the prevalence of COPD is continuing to rise, placing an increased cost-burden and utilisation of hospital bed days on an already overstretched NHS. The advantages of prognostic scoring systems are clear, providing additional information to the clinician about their COPD populations and the information gained would potentially allow clinicians to target resource to the most symptomatic, those most likely to be hospitalised and those most at risk of exacerbation and death.

Although the BODE index, CAT score and SGRQ are used routinely in respiratory based Secondary Care, composite scoring systems are rarely utilised elsewhere, particularly in Primary Care where

the vast majority of COPD patients are managed. The reason for this most likely represents a combination of lack of awareness of the scores existence, lack of time and money to implement any scoring system and, lack of clarity, evidence and financial reward as to how patients should best be managed based on the score results. Historically, COPD risk stratification has been separated into distinct clinical entities, risk of mortality, risk of exacerbation, and risk of increased symptom burden with the outcomes measured being either poor respiratory-specific or general health related quality of life. That these scores are so specific lessens their clinical utility in day to day COPD management.

More recently, research groups have focussed on the utility of risk prediction strategies specifically within Primary Care and have developed prognostic models for use specifically within Primary care. The BARC index, developed by Bloom et al in 2019 used (B) BMI, blood results, (A) age, (R) the respiratory variables, airflow obstruction, exacerbations and smoking and (C) comorbidities to predict mortality at one year in a cohort of patients with known COPD [188]. The cohort used were comprised of Primary Care patients from the UK with data drawn from Primary Care records. The BARC index compared favourably to the BODEx, ADO and DOSE scores at predicting one year mortality and carries the advantage to the COTE index of using only co-morbidity data already recorded in Primary Care. In 2020 Kiddle et al developed and validated a prognostic model for COPD using demographics, BMI, FEV1 and comorbidities which outperformed the Charlson Comorbidity Index at predicting five year mortality after diagnosis. This system, from the same research group, again developed and validated using Primary Care cohorts, uses only data already recorded in Primary Care records and scores are extractable using an electronic calculator [189].

That so many scoring systems have been developed is an encouraging reminder into how the research base in COPD is exponentially expanding. This is a result of new medical, surgical and multidisciplinary based treatment pathways combatting the nihilism that has always existed around COPD patient care. The increasing health and care burden of COPD has helped to drive research by attracting funding sources aimed at reducing costs in the health sector. The disadvantage to this sudden increase in the research base is that it becomes challenging for even those in the speciality to remain up to date and to expect this of the overburdened Primary Care General Practitioners and Practice Nurses is unreasonable and unrealistic. Using the same reasoning, any score used in Primary Care needs to be simple, quick to administrate and easily acted upon with measurable results or it is unlikely to be of practical interest.

Significant nihilism still exists, particularly amongst Primary Care clinicians who, whilst they may be sympathetic to those with COPD, may not believe that improvement is really feasible and as such may be less motivated to pro-actively offer treatment and unwilling to engage with scoring systems they see as time consuming and without clinical benefit. In addition, payment strategies around COPD in Primary Care are currently predominantly based around the documentation of individual investigation results rather than the successful application of risk stratification or management strategies aimed at improving quality of life. The use of yearly spirometry as a QOF outcome is particularly time consuming, necessitating the use of most of the annual review appointment with no financial incentive or reward to alter practice to a more holistic approach to the review.

1.7.4 The optimal management strategy in COPD.

In an ideal world, without financial restraint or time pressures, all patients with COPD would be actively sought out, diagnosed and offered a holistic review to optimise management strategies for their lung disease and co-morbid conditions in a time frame appropriate to their need. This is clearly not a realistic aim in the current NHS climate and so a strategy such as a risk stratification score to select out those at most risk of imminent deterioration (and therefore potential cost to the NHS and social care systems) could be a tool with clinical utility.

The optimal risk stratification score for COPD would be one that is simple, quick and easily interpretable. The object of such an intervention would be to increase the efficiency of clinical time spent with the patient to develop and implement health management strategies. Ideally it would utilise information already routinely recorded for patients in Primary care and could be implemented using an Information Technology database approach. There are always likely to be inaccuracies in large dataset information due to the manner in which data is entered at source, without the data cleaning or quality control seen in research cohorts. Manuel et al explored this concept and proposed that whilst investigators should be aware and if necessary adjust for misclassification errors biasing their study findings, observational databases remain useful resources for research [190]. If a database approach can be shown to work despite these data anomalies then the advantage of a database approach is it avoids using a Clinician's time in any additional data collection, searching or recording.

Intrinsic within the scoring system needs to be a management strategy that can then be acted upon to improve health related quality of life. Managing the impact of co-morbidity in COPD is key to future health status and any management strategy needs to reflect this and encourage

treatment in a holistic manner individualised to each patient. The very encouraging aspect of COPD management is that treatment options such as Pulmonary Rehabilitation and co-morbidity management guidelines are well evidenced, already exist and are currently available in Primary Care but they are underutilised, particularly so in COPD Primary Care patient populations.

Any scoring system used needs to be proven to improve health outcomes when used in an unselective manner in the community (rather than just in the more selective manner of a research cohort) and then be included into National Guidelines to ensure consistency, awareness and education around this approach at a national level. The utilisation of both the scoring system itself and the successful implementation of the therapeutic options it recommends need to be reflected in the financial reward systems in Primary Care to ensure successful changes in practice.

1.7.5 How will this Doctorate move the research field forward?

Research exists suggesting that integrating specialist review of high risk/complex patients into a Primary Care setting may improve high risk patient outcomes and reduce their future healthcare contacts with consequent health care analysis suggesting cost savings [187]. The legacy of these interventions includes upskilling and education of the Primary care MDT and lifting the profile of Respiratory disease within Primary Care [185].

Research is lacking into whether specialist review earlier in the disease course may show similar benefits in terms of confirming diagnoses, patient outcomes and increase access to standard management strategies such as pulmonary rehab. It seems likely that similar benefits may be seen in terms of the upskilling of Primary Care staff and raising the profile of COPD and confidence around its management. Could a proactive holistic Respiratory Specialist review highlight suboptimal control of those comorbidities known to impact negatively on health outcomes in those individuals with COPD, and would this improve quality of life?

Those patients not currently identified as complex or high risk encompass the vast majority of the COPD population, specialist care is expensive and a finite resource, as such, specialist review for all is not a realistic proposition. Over the last five year, models aimed at prognostication in COPD specifically for use in Primary Care have been developed. These have focussed on mortality as an end point for prognostication and a need exists to develop this further using markers of disease or symptomatic deterioration occurring earlier in the disease process.

As yet, a gap in the research remains around the benefits of the modification of these identified comorbid risk factors and whether there is a subset of patients who could be identified early in

their disease process who may benefit over and above other patient subsets from specialist review. Specifically, whether this could delay or decrease subsequent deterioration into highly symptomatic individual individuals requiring high levels of healthcare use in the future.

A database approach:

The initial portion of the research will focus on a database study, aiming to develop a database approach to calculating a COPD risk stratification score in a low risk Primary Care COPD population. The reason to target a 'low risk' group is that these are likely to be the patients with more opportunity to effect management change and try to prevent the deterioration into highly symptomatic individuals, requiring high levels of health care support. The DOSE score is the obvious contender as a start point for this role as it has the advantage of providing information about mortality, hospitalisation and future health status and all its components are routinely recorded in Primary Care records for QOF purposes. Once this database approach is established it can be used in a COPD cohort within the database to establish rates of deterioration in the score over time and its relationship to other clinical outcomes, such as mortality and hospitalisation, providing information regarding the feasibility of its application in a database setting.

In a second phase of the project we will perform a regression analysis aiming to establish whether deterioration in health status within the cohort can be predicted by the pre-existing recorded co-morbidities and social demographics.

A clinical approach:

Running concurrently with the database project we will establish a clinical cohort of COPD patients low risk by DOSE score. We will use this cohort to establish the feasibility of further study on whether a proactive clinical specialist review in Primary Care which aims to optimise disease control using current, established disease management strategies and guidelines could improve subsequent health status.

The combination of this database and clinical approach will provide us with results that will add to the research body to guide us further into the future development and application of an optimal COPD risk stratification and management strategy.

2 DATABASE STUDY: Risk stratification in COPD: Methodology

2.1 Introduction

This study aimed to establish whether comorbidities and social demographics could identify a population of COPD patients, vulnerable to deterioration, prior to their overt clinical manifestation of severe disease. The DOSE score was used to represent COPD disease severity and the study was conducted using real patient records contained in the Hampshire Health Record Analytical Database.

2.1.1 The Hampshire Health Record Analytical Database

The Hampshire Health Record (HHR) is a local clinical database which, at the time of the study, included data from 133 Primary Care Practices across Hampshire, combined with local Secondary Care records. It includes, all entries made in Primary Care during routine patient care, Secondary Care radiology and pathology reports, inpatient, outpatient and A&E attendances imported from Hospital Episode Statistics data, and community care activity data. The database was created to improve clinical information sharing between Primary, Secondary and Integrated Community Services in the County and is managed by NHS South, Central and West Commissioning Support Unit. The Hampshire Health Record Analytical Database (HHRA) is an anonymised version of the HHR using only the Read Coded clinical data. It was created for research, analysis and commissioning support within the local NHS and can be viewed in a pseudonymised format by analysts working directly with the database. All data used for research purposes is extracted in an anonymised format but carries the advantage of being truly representative of the manner in which data is recorded in real patient records.

2.1.2 Using coded data to define disease in the United Kingdom

The National Health Service offers a relatively unique environment to look at coded data in a country where, as only a tiny proportion of medicine is practiced outside of the NHS (and the vast majority of that is communicated to NHS Primary Care), one assumes data collection should be consistent and robust when coded in the NHS Primary Care record. The reality is that there are more than one software systems used to record data in Primary Care and the TRUD coding system, in use throughout the UK during the study period, allows clinicians multiple options in ways to code a diagnosis of COPD or other comorbidities. In this study we opted to use the clinical

expertise of our research team (experienced clinicians based in Primary and Secondary Care) to search the TRUD coding database to create a list of potential ways of coding the various comorbidities used in this study. Clearly, with many thousands of users inputting data into real world databases, any different approach will miss some code diagnoses and risks some false positive by misrepresentative codes (e.g. a search for 'reflux' for GORD will bring up a code describing ureteric reflux, inappropriate for the diagnosis in question). Where researchers use different approaches to their development of coded definitions this will lead to a lack of consistency in different study results. In recognition of this, in 2016, Rimland et al published a protocol for the systematic review of the validation of COPD diagnoses in healthcare databases [191].

The concept that consistency in coded definitions of diagnoses will lead to improvements in result reporting accuracy has been recognised previously in the literature with several research groups suggesting methods to unify and collate coded definitions of various diagnoses [192-194].

2.1.3 Using coded data to define events in the United Kingdom

Defining COPD exacerbations using coded data carries the same risks discussed in section 2.1.2 when defining the disease itself, but with the added complexity of events being missed or duplicated due to timing of coded data entry and the use of prescriptions of steroids and antibiotics as another source of possible record of an exacerbation. An added difficulty when using prescription data, is, that as a part of self-management guidance, individuals with COPD are encouraged to keep a 'rescue pack' of steroids and antibiotics at home. This may mean a database prescription is not always seen in a timeframe aligned to an exacerbation as the individual may already have a stock of medications at home. Prescriptions for antibiotics and steroids will also be seen when these 'rescue packs' are being replaced and this does not necessarily represent a further exacerbation. Various strategies for coding acute exacerbations of have been published [195, 196] using variable timings and combinations of symptoms codes, prescriptions and hospitalisations, with Stone et al recently publishing a systematic review protocol for the validation of acute exacerbation of COPD recording in electronic health records [197]

The Hampshire Health Care Analytical Database has the advantage of combining not only Primary Care records but also hospital inpatient and Emergency Department admission episodes, imported form Hospital Episode Statistics data from the surrounding hospitals. This confers an advantage over Primary Care data alone which has been demonstrated to be around 50% less accurate as a source for reporting hospitalisations for acute exacerbations of COPD [198]. A

disadvantage of the database is it that it only imports data from the hospitals in Hampshire so any hospitalisations out of area will be missed.

Defining deaths through the Hampshire Health Record uses data drawn from Primary Care Read codes rather than from the Office of National Statistics. The HHRA records 'all cause' death and, as the data is anonymised, it cannot be confirmed or further investigated. It is likely that this will carry some degree of error as discussed by Harshfield el al [199], who demonstrated that discrepancies in dates of death between Primary Care and the Office of National Statistics existed in 23.2% of all cases. Most of these discrepancies, however, were related to the exact date of death and in over 90% the difference was less than two weeks in dates. The greatest discrepancies were seen in those with unexplained deaths or with deaths in younger patients. This makes these errors likely to be less impactful on our older study population and as we have looked at the incidence of death over several years' time period any inaccuracies are likely to be minimal.

2.2 Study Objectives

Objective 1: To evaluate the rate of change in DOSE score in a COPD patient cohort in the Hampshire Health Record Analytical database over five years and separate this cohort into two subgroups based on their rate of deterioration.

Objective 2: To identify Primary Care coded clinical, social and demographic characteristics associated with the more rapidly deteriorating patient group.

Objective 3: To create a risk stratification model for early stage COPD, applicable in Primary Care, utilising Read code entries within patient records.

2.3 Ethical considerations

Ethical approval was obtained from the University of Southampton. Protocols for this study were approved by the Hampshire Health Care Record Advisory Group for the use within the HHRA.

2.4 Methodology

2.4.1 Using Read coded clinical data, a COPD database cohort can be identified and separated into a rapidly and slowly deteriorating cohort.

The HHRA COPD patient population was established to be all those patients within the HHRA who, as of 1st January 2010, had received a Read code diagnostic of COPD (Appendix 2. The Read codes and terms used to define diagnosis of COPD.). At the point of data extraction, records were available for the five years following the 1st January 2010. Patients were excluded from the study if they moved to a Primary Care Practice that did not to submit to the HHRA during the study period. All Read code lists were compiled and mutually agreed upon by myself, another Specialist Respiratory Registrar and a General Practitioner with a specialist respiratory interest.

DOSE score was used as our marker of disease severity which required establishing mMRC score, FEV_1 percentage predicted, smoking status and exacerbation rate from the patient records. Specific Read codes denote MRC score, FEV_1 and smoking status as seen in, Appendix 3. The Read codes and terms used to define mMRC score, FEV1 and smoking status. Determining the number of exacerbations in the preceding year was more complex as an exacerbation may be recorded in multiple different ways within the patient record. We developed an algorithm using combinations of specific Read codes denoting 'exacerbation of COPD', as well as surrogate Read codes, for example, those denoting respiratory tract infections or symptoms suggestive of a COPD exacerbation in combination with antibiotic and steroid prescriptions (Appendix 4. The Read codes, Terms and algorithm used to define exacerbations).

Whilst a specific Read code does denote FEV_1 percentage of predicted, an FEV_1 volume may also or alternatively be recorded. If both existed, the FEV_1 percentage of predicted was used but in the case where there was only a volume documented then the percentage predicted was calculated using the following formulae;

Male: FEV_1 volume/ ((4.30 *height at start of study period) – (0.029 *age at start of study period) – 2.49) *100

Female: FEV_1 volume/ ((3.95 *height at start of study period) – (0.025 *age at start of study period) – 2.60) *100

Any FEV_1 volume results recorded to be ≤0.2L or ≥7L were assumed to be erroneous and excluded from the dataset as were any FEV_1 percentage of predicted values ≤10% or ≥140%.

The date of the DOSE score required definition as the exacerbation rate is calculated from the preceding twelve months of data. The date of the first DOSE score generated per patient was referred to as 'Annual Review 1' and its date was defined by the first FEV_1 data entry recoded on or after 1st January 2010. Failing any FEV_1 Read code entries after 1st January 2010, Annual Review 1 was defined by the date of the first MRC score data entry.

DOSE scores were generated at Annual Review 1 in all patients with sufficient data to make it possible. The exacerbation component of the score was calculated from the twelve months of data preceding Annual Review 1. The MRC score and smoking status were ascertained using the Read code chronologically closest to the Annual Review 1 date, from the data spanning the period twelve months prior to Annual Review 1.

We considered administrative staff in Primary Care Practices may have entered QOF data days or months after it had been obtained by clinical staff at the patient visit. To allow for this potential wider timeframe, we compared the difference in DOSE score values and total DOSE score numbers for the cohort using the method described above and then using MRC score and smoking status data from the twelve months preceding AND the three months following Annual Review 1. The number and spread of scores produced were comparable between the two methods and consequently all DOSE scores reported in the results are calculated using data from twelve months preceding the Annual Review date only.

Each patient for whom an Annual Review 1 could be generated, was followed for four years post Annual Review 1 or until 28th February 2015, whichever fell soonest. Any patient in whom insufficient data existed to calculate an Annual Review 1 (i.e. no spirometry or MRC score Read code entries recorded from 1st January 2010 until 31st December 2014) was followed for four years from 1st January 2010.

A DOSE score of greater than or equal to four allocated a patient to the 'high' category (representing a patient with severe disease) and a score of less than or equal to three, the 'low" category (representing a patient with less severe disease) as per Jones et al [56]. Whilst some patients for whom we were able to establish an Annual Review date (i.e. they had an MRC and/or spirometry recorded) did not have all elements of the DOSE score, we were able to ascertain a partial DOSE score for them. This score was termed 'established' and the patients were included in the study cohort if the established score either already fell into the 'high' category, or, was a low score that would remain low even if the highest possible score were obtained in the missing score components.

For the subsequent analysis we used only those patients with an 'established' first low DOSE score (≤3) as our 'low DOSE initial cohort'. Patients excluded were those whom did not have an 'established' DOSE score prior to 1st March 2011, and those who had moved to a Primary Care Practice that did not submit to the Hampshire Health Record prior to the end of their follow up period.

Additional Annual Review dates were generated for each patient in the same manner as Annual Review 1 each time an additional spirometry or MRC score Read Code value was recorded. Each Annual Review date was at least twelve months from the preceding Annual Review. The Read code approximation of the DOSE score was reapplied at each annual review, for four years post Annual Review 1 (or until 28th February 2015) on our low DOSE initial cohort. We expected to collect a maximum of three data points for each patient, given, each clinical COPD Annual Review, in which spirometry is recorded, tends to be thirteen or fourteen months apart (see Figure 2-1).

Over the subsequent study period for each patient we also collected Read code data relating to:

- Days spent as an inpatient in hospital (Appendix 5. The Read codes terms used to define inpatient admission)
- Emergency department visits (Appendix 5. The Read codes terms used to define inpatient admission)
- Death (all-cause mortality)

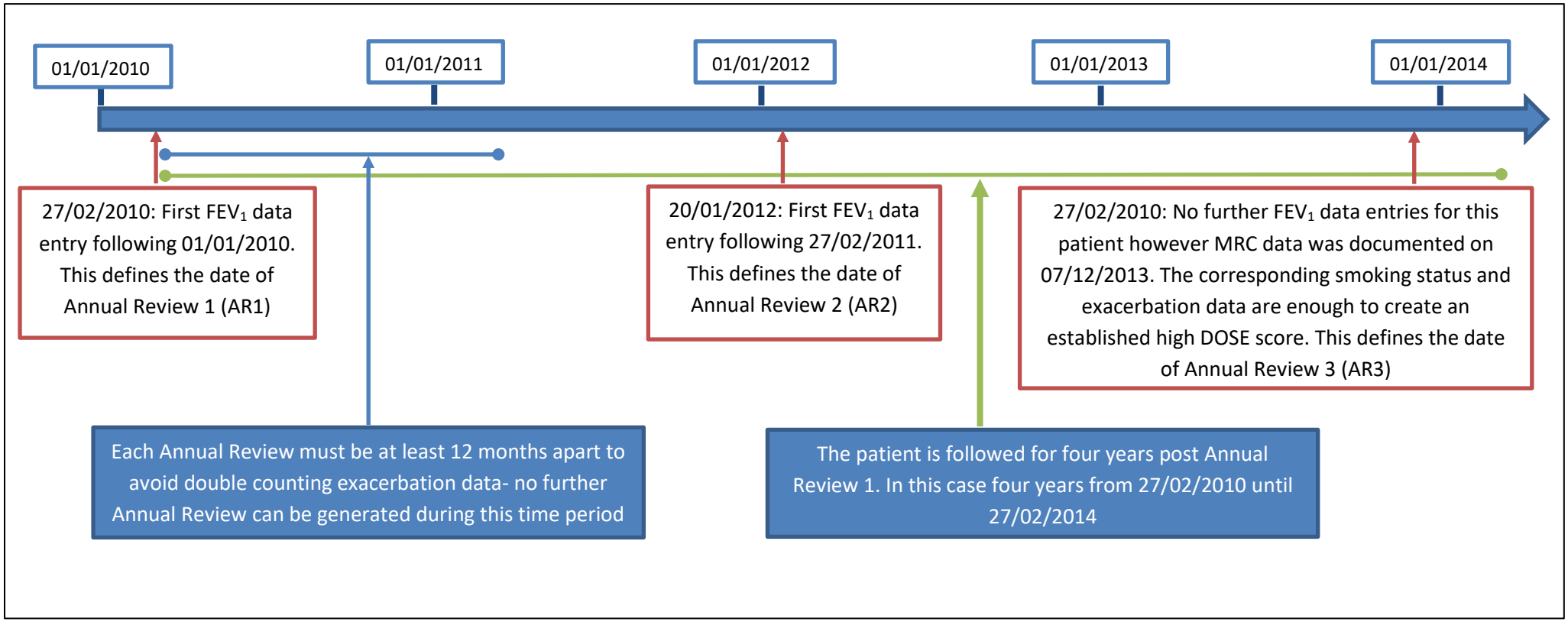
The low DOSE initial cohort were allocated to a 'rapidly deteriorating subgroup' or 'slowly deteriorating subgroup' where the 'rapidly deteriorating subgroup' consisted of patients experiencing any one of the following outcomes:

- Any patient who required an Emergency Department Visit or Secondary Care admission for COPD treatment during the study period.
- Any patient in whom, at any point, DOSE score declined into the 'high risk' group of ≥4
- Any patient in whom DOSE score increased by two points or more from the first to the final recorded DOSE score.
- Death during the follow up period (all cause)

Death as an outcome is self explanatory when allocating an individual to a more rapidly deteriorating subgroup and there is a significant body of research demonstrating how an exacerbation requiring a hospital admission is a poor prognostic marker in a patient with COPD.

Whilst a DOSE score is not a health outcome in itself, a deterioration into the 'high risk' score of ≥4 increases an individual's risk of the negative health outcomes discussed previously such as five year mortality , type II respiratory failure and hospital admission in the following twelve months. A deterioration in DOSE score (within the 0-3 score range) was used as the final poor health outcome measure. We acknowledge that this again, is not in itself an evidenced poor health outcome however, based on the mortality data in seen in the research done by Sundh et al. a difference was seen in the mortality rates for those with a score 4-5 and 6-7. As we are looking for early deteriorations in heath outcome, it seems reasonable to use an early deterioration in DOSE score (made up of components either poor health outcomes themselves or well evidenced to adversely impact upon health outcome as the score increases) as a surrogate marker of early disease deterioration.

Figure 2-1 The database study timeline in an example patient.



2.4.2 Certain Primary Care coded clinical, social and demographic characteristics are associated with the more rapidly deteriorating subgroup.

The presence of Read codes approximating the following diagnoses and social demographics were established for all individuals in the HHRA COPD patient population.

- Age, gender, ethnicity, lower layer superoutput area (a surrogate marker of deprivation decile) and the total number of historical comorbidities (of those detailed below) were recorded as stated at the closest documented point to 1st January 2010.
- Anxiety and/or depression, asthma, bronchiectasis, cardiac failure, cerebrovascular disease, chronic kidney disease, connective tissue disease, Cor Pulmonale, dementia, diabetes, gastro-oesophageal reflux disease, hyperlipidaemia, hypertension, ischaemic heart disease, lung cancer, obstructive sleep apnoea, osteoporosis, peripheral vascular disease, pulmonary fibrosis and rhinitis/sinus disease were recorded as present if they had ever been documented prior to 1st January 2010. In our initial data interrogation for the comorbidities we included the coded demographics of being housebound or living alone (both of which have specific Read Codes) and coded data for Mini Mental State examination, however on initial analysis of the data it became apparent that these codes are utilised so rarely by Primary Care clinicians that they did not provide any meaningful data and consequently the variables were excluded from the subsequent analysis.
- The presence of, and number of episodes of pneumonia in the two years prior to 1st January 2010.
- The pathology data representing a full blood count in the two years prior to 1st January 2010, if the eosinophil count represented greater than 2% of the total lymphocyte count (as a surrogate marker of sputum eosinophilia [70]).
- BMI and certain drug prescriptions were recorded if they had ever been documented in the twelve months prior to 1st January 2010. If more than one BMI measurement was recorded in the twelve months prior to 1st January 2010 then the most recent measurement was used. The prescription drugs recorded included; any nebulised short acting beta agonist (SABA) or short acting muscarinic antagonist (SAMA) and any of the following inhaled drugs including; SAMA, single agent long acting beta agonist (LABA) or long acting muscarinic antagonist (LAMA), combination LAMA/LABA, single agent inhaled corticosteroid (ICS), each of the named and generic combination ICS/LABA inhaled preparations. The combination ICS/LABA inhaled preparations Symbicort, Fostair, Seretide, Relvar Ellipta and Flutiform were available at the time of study.

For those patients in whom we were able to generate an Annual Review Date, these variables were also recorded over the same timeframes but using Annual Review Date 1 rather than 1st January 2010 as a reference point. The exception to this were age, gender, ethnicity and lower layer superoutput area which do not change with time.

To ease the interpretation and clinical utility of the results, age, BMI and drug prescriptions were grouped into the following categories;

Age:

- <50 years
- 50-59 years
- 60-69 years
- 70-79 years
- 80-89 years
- >90 years

BMI:

- <18
- 18-24
- 25-29
- 30-34
- >35

Drug prescriptions:

- Inhaled SABA
- Inhaled SAMA
- Any inhaled LABA or LAMA
- Any single agent ICS device
- Any combination ICS/LABA device
- Any nebulised bronchodilator

Specific Read codes denote BMI, but the data may also or alternatively be entered in its raw form e.g. weight and height. To minimise potential user input error, where possible, we calculated the BMI from source data using the formula; BMI = weight (kg)/height $(m)^2$. Any values calculated at greater than 60 or less than 12 were felt to most likely be erroneous and were excluded from the

data.

In the low DOSE initial cohort, bivariate analysis was used to establish whether each clinical characteristic was associated with an increased likelihood of the patient going on to be allocated into the rapidly deteriorating subgroup.

2.4.3 The development of a risk stratification model for early stage COPD, applicable in Primary Care, utilising Read code entries within patient records.

A risk stratification model was developed using logistic regression modelling in the individuals in whom we were able to generate an established low DOSE score before 1st March 2011, i.e. the low DOSE initial cohort. We also excluded those individuals in whom we did not have complete data for all variables (This only affected individuals without the continuous variables, deprivation decile and BMI).

We expected age to have the strongest association with the rapidly deteriorating subgroup. For the model to have the potential to be developed into a management template to attempt to modify these identified risk factors, its variables needed to be, not just strongly associated, but also potentially clinically modifiable. By using the results of the logistic regression analysis in conjunction with clinical judgement as to which clinical variables had the greatest potential for optimisation, we selected out those variables most appropriate for use in a clinically applicable Primary Care model. Using these variables, we developed an alternative model as an example of the type of model, useful in Primary Care, to identify those patients at high risk of allocation to the rapidly deteriorating subgroup, using clinically modifiable variables in whom we could potentially intervene to optimise these variables and establish if this could alter health outcomes in a real world patient group.

The variables chosen for the alternative model, shown in

Figure 3-4, were based on the clinical judgement and experience of the author based on the following logic:

- **Deprivation Decile**- those living in the most deprived areas may be less likely to be able to access Pulmonary Rehabilitation courses due to work commitments or transport accessibility.
- **BMI**- a low BMI may be addressed with education around nutrition and nutritional supplements if appropriate.
- **History of pneumonia**- whilst this cannot be altered it can be considered a prompt to ensure patients have been offered (or re-offered) and educated upon the importance of pneumococcal and influenza vaccination. It is also an opportunity to consider the possibility and treatment of gastro-oesophageal reflux disease as a risk factor for the development of further episodes of pneumonia.
- **Blood eosinophils > 2%**- the presence of a raised eosinophil count suggests the possibility of either a misdiagnosis of COPD in the case of asthma with fixed airflow obstruction or the possibility of asthma- COPD overlap disease. Either of these disease modalities are likely to benefit from an inhaled steroid which may not be prescribed in the current COPD prescribing guidance regime [8].
- **History of anxiety or depression**- as previously discussed, there is well documented evidence for poorer outcomes and quality of life indicators for those experiencing mental health disease however there are many pharmacological and non-pharmacological treatments available. The inclusion of this variable in the alternative model provides the opportunity to ensure that all treatment possibilities have been offered and made as accessible as possible to the patient concerned.
- **Prescription of nebulised bronchodilators**- the prescription of domiciliary nebulised bronchodilators suggests a patient with either a heavy symptom burden. This may not be modifiable, but it offers the opportunity to ensure that a lack of education and/or skills to manage breathlessness symptoms in this patient are not a contributing factor. If the latter is the case, it often leads to a reluctance to exercise and the consequent negative spiral into muscle wasting and cachexia described in section 1.4.6, as well as poorer quality of life. This may be modifiable with the education and breathlessness management techniques taught in Pulmonary Rehabilitation.

2.5 Statistical Analysis

Throughout the study, all results were analysed using SPSS version 22 and a p value of <0.05 was considered statistically significant. Given the 'real world' nature of the HHRA it was likely there would be incomplete or missing data points and variables. Despite this we used complete case

analysis for all variables rather than imputation techniques to keep the methods real world applicable. Bivariate analysis using Chi-squared test, independent T-test or Mann-Whitney U test as appropriate were used to establish any significance in the baseline distribution of variables between the initial cohorts and rapidly/slowly deteriorating subgroups. Odds ratios have also been added at the suggestion of the examiners.

Forwards and backwards stepwise logistic regression methods and consideration of adjustment factors and potential confounders were used to establish the combination of variables which had the strongest association with the rapidly deteriorating subgroup with the final logistic regression analysis using forward conditional modelling.

3 DATABASE STUDY: Risk stratification in COPD: Results and Discussion

3.1 Using Read coded clinical data, a COPD database cohort can be identified and separated into rapidly and slowly deteriorating subgroups

3.1.1 Results

On 1st January 2010, 13608 patients had a Read code diagnostic of COPD and these individuals made up the HHRA COPD patient population. The process of establishing the low DOSE initial cohort is illustrated using the flowchart in Figure 3-1. During the study period (four years post Annual Review 1), 181 patients moved to a Primary Care Practice which does not submit to the HHRA and were therefore lost to follow up. 5567 patients had insufficient data to create a DOSE score prior to 1st March 2011 (i.e., within the first fourteen months of the study) so were removed. This left 7860 remaining patients, 57.8% of the initial COPD patient population. Of these, 970 patients were calculated to have a high DOSE score of ≥4 at Annual Review 1, leaving 6890 COPD patients with a baseline low DOSE score which comprised our low DOSE initial cohort.

The HHRA COPD patient population characteristics are presented in Table 3-1 and Table 3-2 which display the baseline population demographics and co-morbidities respectively. The tables include the results of a bivariate analysis displaying any difference between those included and excluded from the study and the population as a whole. The characteristics of the those included were similar to those excluded from the study, with the those included representing a group of individuals, predominantly age 60-80 years, similar in deprivation rates, gender and subsequent rates of hospitalisation to those excluded from the study. Where FEV_1 and MRC score were recorded these were very similar between the two groups and fell in the 'moderate' range for each measurement at 58-59% and 2.0 respectively. Co-morbidity rates were consistent across both groups with a median co-morbidity number of 2.0 (confidence interval 3.0) demonstrating a relatively co-morbid group of individuals. Those co-morbidities likely to lead to difficulty with service engagement such as dementia, cerebrovascular disease and anxiety or depression were all slightly higher in those excluded from the study but overall rates of anxiety or depression in both groups were high (dementia 1.1% vs 3.3% $p < 0.001$, cerebrovascular disease 8.8% vs 10.4% $p=0.001$, anxiety or depression 35.5% vs 38.9% $p<0.001$). Rates of asthma were high in both

groups, more so in those included with rates of 51.5% and 44.3% respectively (p <0.001) and this finding was mirrored in rhinosinusitis rates, 15.3% and 12.3% (p <0.001).

Figure 3-1 Generation of the low DOSE initial cohort: Flow chart demonstrating the formation of the low DOSE initial cohort.

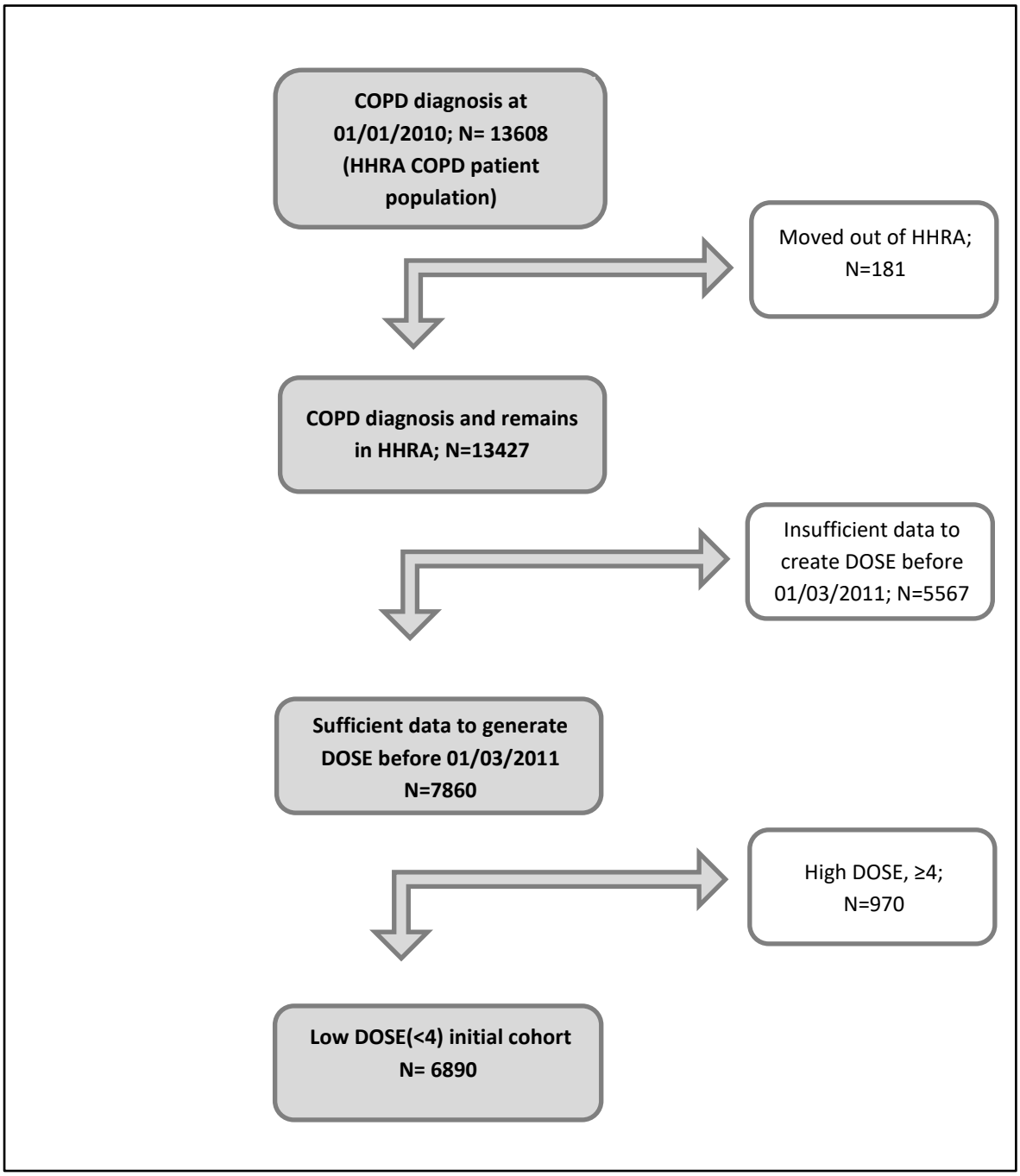


Table 3-1 Description of the HHRA COPD patient population characteristics.

Table describing the characteristics of the HHRA COPD patient population displaying differences in the characteristics of those included and excluded from the study. See Table 3-2 for key**.**

Clinical characteristics established at baseline (1st January 2010) *, **	HHRA COPD patient population, excluding those who moved out of area (N=13427)		Patients included in the study; DOSE score generated before 01/03/2011 (N=7860)		Patients excluded from the study; insufficient data to generate a DOSE score before 01/03/2011 (N=5567)		p value ***
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	
Gender							<0.001
Female	6253 (46.6%)		3547 (45.1%)		2706 (48.6%)		
Male	7174 (53.4%)		4313 (54.9%)		2861 (51.4%)		
Age							<0.001
<50	555 (4.1%)		232 (3.0%)		323 (5.8%)		
50-59	1694 (12.6%)		906 (11.5%)		788 (14.2%)		
60-69	4051 (30.2%)		2485 (31.6%)		1566 (28.1%)		
70-79	4323 (32.2%)		2778 (35.3%)		1545 (27.8%)		
80-89	2484 (18.5%)		1348 (17.2%)		1136 (20.4%)		
90+	320 (2.4%)		111 (1.4%)		209 (3.8%)		
Deprivation decile (10 is most deprived)*		7.0 (5.0)		7.0 (5.0)		6.0 (5.0)	0.558
BMI*							0.001
<18	255 (3.5%))		163 (2.9%)		97 (3.8%)		
18 to 24	2314 (31.9%)		1801 (31.7%)		895 (35.0%)		
25 to 29	2447 (33.7%)		1963 (34.5%)		799 (31.2%)		
30 to 34	1429 (19.7%)		1149 (20.2%)		487 (19.0%)		
>35	812 (11.2%)		611 (10.7%)		279 (10.9%)		
Smoking Status*							<0.001
Current smoker	4537 (42.7%)		2800 (40.1%)		1737 (47.8%)		
Ex smoker	5160 (48.6%)		3610 (51.7%)		1550 (42.7%)		
Never smoker	924 (8.7%)		577 (8.3%)		347 (9.5%)		
MRC breathlessness score		2.0 (1.0)		2.0 (1.0)		2.0 (1.0)	<0.001
FEV_1 percentage of predicted		59.3 (28.0)		59.8 (19.7)		58.7 (20.1)	0.038
Exacerbation number in the preceding twelve months		0.7 (1.0)		0.0 (1.0)		0.0 (1.0)	<0.001
Initial DOSE score value*		1.6 (1.0)		1.0 (1.0)		1.0 (1.0)	<0.001
Initial low DOSE score (<4)	10264 (88.6%)		6890 (87.7%)				
Hospitalisation within 4 years	4435 (33%)		2602 (33.1%)		1833 (32.9%)		0.829
Death within 4 years	2375 (17.7%)		1078 (13.7%)		1297 (23.3%)		<0.001

Table 3-2 Description of the HHRA COPD patient population comorbidities and prescriptions. Table describing the comorbidities and respiratory prescriptions of the HHRA COPD patient population with a bivariate analysis of the characteristics of those included and excluded from the study cohort.

Comorbidities and prescriptions	HHRA COPD patient population, excluding those who moved out of area (N=13427)		Patients included in the study; DOSE score generated before 01/03/2011 (N=7860)		Patients excluded from the study; insufficient data to generate a DOSE score before 01/03/2011 (N=5567)		p value ***
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	
Number of comorbidities		2.6 (3.0)		2.0 (3.0)		2.0 (3.0)	<0.001
Pneumonia	598 (4.5%)		311 (4.0%)		287 (5.2%)		0.001
Pulmonary Fibrosis	197 (1.5%)		121 (1.5%)		76 (1.4%)		0.408
Asthma	6511 (48.5%)		4046 (51.5%)		2465 (44.3%)		<0.001
Bronchiectasis	533 (4.0%)		309 (3.9%)		224 (4.0%)		0.787
Lung Cancer	114 (0.8%)		51 (0.6%)		63 (1.1%)		0.003
Obstructive Sleep Apnoea	114 (0.8%)		69 (0.9%)		45 (0.8%)		0.665
Rhinosinusitis	1890 (14.1%)		1205 (15.3%)		685 (12.3%)		<0.001
Gastro Oesophageal Reflux	1337 (10.0%)		826 (10.5%)		511 (9.2%)		0.011
Connective Tissue Disease	319 (2.4%)		188 (2.4%)		131 (2.4%)		0.885
Anxiety Or Depression	4955 (36.9%)		2789 (35.5%)		2166 (38.9%)		<0.001
Ischaemic Heart Disease	2594 (19.3%)		1555 (19.8%)		1039 (18.7%)		0.105
Osteoporosis	871 (6.5%)		477 (6.1%)		394 (7.1%)		0.019
Heart Failure	841 (6.3%)		452 (5.8%)		389 (7.0%)		0.004
Cor Pulmonale	71 (0.5%)		27 (0.3%)		44 (0.8%)		<0.001
Hypertension	5518 (41.1.%)		3362 (42.8%)		2156 (38.7%)		<0.001
Hyperlipidaemia	2323 (17.9%)		1460 (18.6%)		863 (15.5%)		<0.001
Cerebrovascular Disease	1271 (9.5%)		690 (8.8%)		581 (10.4%)		0.001
Peripheral Vascular Disease	767 (5.7%)		458 (5.8%)		309 (5.6%)		0.497
Chronic Kidney Disease	2023 (15.1%)		1226 (15.6%)		797 (14.3%)		0.041
Dementia	274 (2.0%)		88 (1.1%)		186 (3.3%)		<0.001
Diabetes	1804 (13.4%)		1079 (13.7%)		725 (13.0%)		0.238
Blood eosinophils ≥2%	5963 (44.4%)		3474 (44.2%)		2489 (44.7%)		0.557
Prescriptions in the preceding twelve months:							
Nebulised bronchodilator	1002 (7.5%)		540 (6.9%)		462 (8.3%)		0.002
Single Agent ICS	3715 (27.7%)		2443 (31.1%)		1272 (22.8%)		<0.001
ICS/LABA combination	4502 (33.5%)		3035 (38.6%)		1467 (26.4%)		<0.001
Inhaled LABA or LAMA	4196 (31.3%)		2889 (36.8%)		1307 (23.5%)		<0.001
Inhaled SAMA	2506 (18.7%)		1704 (21.7%)		802 (14.4%)		<0.001
Inhaled SABA	9032 (67.3%)		5984 (76.1%)		3048 (54.8%)		<0.001

Key for Table 3-1 and Table 3-2

**HHRA COPD patient population: complete case data for all clinical characteristics excepting MRC score (55.7%), FEV1 percentage predicted (55.5%), smoking status (79.1%), Deprivation decile (missing data for seven individuals) and BMI (61.4%)*

***Patients included in the study (DOSE score generated before 01/03/2011): complete case data for all clinical characteristics excepting MRC score (68.7%), FEV1 percentage predicted (70.4%), smoking status (88.9%), Deprivation decile (missing data for two individuals) and BMI (72.4%)*

****p values express the statistical significance between clinical characteristic prevalence in the study cohort and in those with insufficient data to generate a DOSE score before 01/03/2011. p values calculated using Chi squared test for categorical variables, Independent T-tests for continuous variables with a normal distribution (FEV1 percentage predicted) and Mann-Whitney test for continuous variables not normally distributed (comorbidity number, exacerbation frequency, MRC score, deprivation decile, DOSE score).*

Those excluded from the study had marginally lower BMI measurements (p = 0.001) and were significantly more likely to be current smokers when compared with those included (47.8% vs 40.1%, p<0.001). Those excluded from the study were significantly less likely to be on optimal inhaled therapy (LABA or LAMA 36.8% vs 23.5% p <0.001, ICS/LABA 38.6% vs 26.4% p <0.001) but significantly more likely to be on nebulised therapy (6.9% vs 8.3% p =0.002). Both groups had high rates of single agent ICS prescription although this was also significantly higher in those included in the study (31.1% vs 22.8% p <0.001). The most striking difference noted was in the mortality rates during the study period which were significantly lower in those included with a rate of 13.7% vs 23.3% in those excluded from the study (p <0.001)

When those in the study were separated by DOSE score into the low DOSE initial cohort and those with a high DOSE score, the high DOSE patients had a similar spreads of age and gender but represented a more co-morbid group with higher rates of most co-morbidity prevalence and respiratory medication prescription than in the low DOSE initial cohort. Table 3-3 and Table 3-4 display the results of a bivariate analysis demonstrating the demographic and co-morbidity differences between those with a high DOSE score and the low DOSE initial cohort. Pneumonia rates were particularly different with a rate of 13.6% in the low DOSE initial cohort and 30.9% in those with a high DOSE score (p <0.001). The exceptions to this were rhinitis/ sinus disease and hypertension prevalence which were both significantly higher in the low DOSE initial cohort (16.2% vs 12.7%, p =0.005 and 44.2% vs 37.8%, p <0.001 respectively). Hyperlipidaemia, connective tissue disease and chronic kidney disease had equal prevalence (19.0% vs 18.7%, p =0.793, 2.5% vs 2.4%, p =0.814 and 16.2% vs 16.0%, p =0.872 respectively).

Of the 6890 individuals in the low DOSE initial cohort, 3302 (48%) went on to experience one of the outcomes presented in Table 3-6. Hospitalisation was the most common occurrence, with 68% of the rapidly deteriorating subgroup requiring a respiratory related Emergency Department attendance or hospital admission. 28% of this subgroup died within the study period with 23% showing an increase in DOSE score into a high risk score of ≥4 and 22% showing an increase in DOSE score of 2 points or more.

In section 2.4 we detailed our concern that data may not be entered contemporaneously to the date of the patient visit to Primary Care. As discussed in section 2.4, we compared the difference in DOSE score values and total DOSE score numbers generated for those included in the study using data from the twelve months preceding Annual Review 1 only; and using MRC score and smoking status data from the twelve months preceding AND the three months following Annual Review 1. Table 3-5 illustrates the difference this created in the numbers of patients with enough

data to be included in both the study and low DOSE initial cohort. As the table demonstrates, this difference was minimal when the data collection window for each Annual Review was broadened from the 12 months preceding review only, to include the subsequent three months. As such, all calculations used data collected from the preceding 12 months only.

Table 3-3 Description of the characteristics of those included in the study.

A bivariate analysis comparing the characteristics of those with a high DOSE score and the low DOSE initial cohort

Clinical characteristics established at baseline (1st January 2010) *	Low DOSE initial cohort Score < 4 (N=6890) N	Median (IQR)	Those with a high DOSE score, ≥ 4 (N=970) N	Median (IQR)	Odds ratio (with 95% CI)	p value**
Gender						
Female	3119 (45.3%)		428 (44.1%)		0.95 (0.83, 1.09)	0.502
Male	3771 (54.7%)		542 (55.9%)		1.00	
Age						0.704
<50	207 (3.0%)		25 (2.6%)		1.00	
50-59	794 (11.5%)		112 (11.5%)		0.86 (0.54, 1.36)	
60-69	2161 (31.4%)		324 (33.4%)		0.81 (0.52, 1.24)	
70-79	2454 (35.6%)		324 (33.4%)		0.91 (0.59, 1.41)	
80-89	1177 (17.1%)		171 (17.6%)		0.83 (0.53, 1.30)	
90+	97 (1.4%)		14 (1.4%)		0.84 (0.42, 1.68)	
Deprivation decile (10 is most deprived)		7.0 (5.0)		6.0 (5.0)		<0.001
BMI*						<0.001
<18	114 (2.3%)		49 (7.2%)		0.38 (0.27, 0.55)	
18 to 24	1548 (30.9%)		253 (37.2%)		1.00	
25 to 29	1774 (35.4%)		189 (27.8%)		1.53 (1.26, 1.87)	
30 to 34	1039 (20.8%)		110 (16.2%)		1.54 (1.22, 1.96)	
>35	531 (10.6%)		80 (11.7%)		1.08 (0.83, 1.42)	
Current Smoking Status						<0.001
Yes	2465 (37.4%)		578 (62.0%)		1.00	
No	4128 (62.6%)		355 (38.0%)		0.37 (0.32, 0.42)	
MRC breathlessness score						<0.001
0-1	4417 (65.2%)		29 (3.0%)		1.00	
2	1723 (25.4%)		190 (19.6%)		0.06 (0.04, 0.09)	
3	605 (8.9%)		526 (54.3%)		0.01 (0.01, 0.01)	
4	30 (0.4%)		223 (23.0%)		0.001 (0.001, 0.001)	
FEV_1 percentage of predicted						<0.001
>50	4937 (73.6%)		144 (15.9%)		1.00	
30-49	1620 (24.2%)		447 (49.3%)		0.11 (0.09, 0.13)	
<30	147 (2.2%)		316 (34.8%)		0.01 (0.01, 0.02)	
Exacerbation number in the preceding twelve months						<0.001
0-1	5958 (86.5%)		401 (41.3%)		1.00	
2-3	822 (11.9%)		343 (35.4%)		0.16 (0.14, 0.19)	
>3	110 (1.6%)		226 (23.3%)		0.03 (0.03, 0.04)	
Initial DOSE score value		1.0 (2.0)		4.0 (1.0)		
Hospitalisation within 4 years	2047 (29.7%)		627 (64.6%)		0.29 (0.25, 0.33)	<0.001
Death within 4 years	848 (12.3%)		319 (32.9%)		0.29 (0.25, 0.33)	<0.001

Key for Table 3-3 and Table 3-4 **All individuals: complete case data for all clinical characteristics with the exception of MRC score (98.5%), FEV1 percentage predicted (96.8%), smoking status (95.8%), Deprivation decile (missing data for one individual) and BMI (72.4%)*

***p values calculated using Chi squared test for categorical variables and Mann-Whitney test for continuous variables not normally distributed (comorbidity number and deprivation decile). Odds ratios presented for categorical variables.*

Table 3-4 Description of the comorbidities and respiratory prescriptions of those included in the study.

A bivariate analysis comparing the of those with a high DOSE score and the low DOSE initial cohort (see Table 3-3 for key)

Comorbid conditions/respiratory prescriptions at baseline (1st January 2010) *	Low DOSE initial cohort Score < 4 (N=6890)		Those with a high DOSE score, ≥ 4 (N=970)		Odds ratio (with 95% CI)	p value**
	N	Median (IQR)	N	Median (IQR)		
Number of comorbidities		2.0 (3.0)		3.0 (2.0)		<0.001
Pneumonia	934 (13.6%)		300 (30.9%)		0.35 (0.30, 0.41)	<0.001
Pulmonary Fibrosis	103 (1.5%)		21 (2.2%)		0.69 (0.43, 1.10)	0.119
Asthma	3498 (50.8%)		579 (59.7%)		0.70 (0.61, 0.80)	<0.001
Bronchiectasis	266 (3.9%)		59 (6.1%)		0.62 (0.46, 0.83)	0.001
Lung Cancer	45 (0.7%)		9 (0.9%)		0.70 (0.34, 1.44)	0.335
Obstructive Sleep Apnoea	55 (0.8%)		20 (2.1%)		0.38 (0.23, 0.64)	0.000
Rhinosinusitis	1116 (16.2%)		123 (12.7%)		1.33 (1.09, 1.63)	0.005
Gastro Oesophageal Reflux	757 (11.0%)		125 (12.9%)		0.83 (0.68, 1.02)	0.080
Connective Tissue Disease	172 (2.5%)		23 (2.4%)		1.05 (0.68, 1.64)	0.814
Anxiety Or Depression	2412 (35.0%)		445 (45.9%)		0.64 (0.55, 0.73)	<0.001
Ischaemic Heart Disease	1348 (19.6%)		236 (24.3%)		0.76 (0.65, 0.89)	0.001
Osteoporosis	408 (5.9%)		98 (10.1%)		0.56 (0.44, 0.71)	<0.001
Heart Failure	387 (5.6%)		92 (9.5%)		0.57 (0.45, 0.72)	<0.001
Cor Pulmonale	16 (0.2%)		18 (1.9%)		0.12 (0.06, 0.24)	<0.001
Hypertension	3045 (44.2%)		367 (37.8%)		1.30 (1.13, 1.49)	<0.001
Hyperlipidaemia	1310 (19.0%)		181 (18.7%)		1.02 (0.86, 1.22)	0.793
Cerebrovascular Disease	619 (9.0%)		107 (11.0%)		0.80 (0.64, 0.99)	0.040
Peripheral Vascular Disease	387 (5.6%)		86 (8.9%)		0.61 (0.48, 0.78)	<0.001
Chronic Kidney Disease	1115 (16.2%)		155 (16.0%)		1.02 (0.85, 1.22)	0.872
Dementia	90 (1.3%)		19 (2.0%)		0.66 (0.40, 1.09)	0.106
Diabetes	973 (14.1%)		156 (16.1%)		0.86 (0.71, 1.03)	0.103
Blood eosinophils ≥2%	2986 (43.3%)		521 (53.7%)		0.66 (0.58, 0.75)	<0.001
Prescriptions in the preceding twelve months:						
Nebulised bronchodilator	332 (4.8%)		269 (27.7%)		0.13 (0.11, 0.16)	<0.001
Single Agent ICS	2010 (29.2%)		293 (30.2%)		0.95 (0.82, 1.10)	0.508
ICS/LABA combination inhaler	2595 (37.7%)		576 (59.4%)		0.41 (0.36, 0.47)	<0.001
Inhaled LABA or LAMA	2394 (34.7%)		601 (62.0%)		0.33 (0.28, 0.38)	<0.001
Inhaled SAMA	1359 (19.7%)		254 (26.2%)		0.69 (0.59, 0.81)	<0.001
Inhaled SABA	5090 (73.9%)		875 (90.2%)		0.31 (0.25, 0.38)	<0.001

Table 3-5 Differences in study numbers using alternative timeframes.

	Number of individuals included using data points within:	
	The 12 months preceding Annual Review 1 only	The 12 months preceding and 3 months following Annual Review 1
Patients included in the study	7860 (100%)	8028 (100%)
Individuals with sufficient data to generate AR 2	6840 (87%)	6492 (87.1%)
Individuals with sufficient data to generate AR 3	5193 (66.1%)	5297 (66.0%)
Low DOSE initial cohort	6890 (87.7%)	7033 (87.6%)

Table 3-6 COPD Outcome Frequencies.

Table demonstrating the frequency of each outcome allocating patients to the rapidly deteriorating subgroup.

Outcome (occurring over the four years from baseline)	Frequency of outcome (N=3007)
Death during the study period	848 (28.2%)
Hospitalisation during the study period	2047 (68.1%)
DOSE score increase of 2 or more between initial and final DOSE score	672(22.3%)
Subsequent 'high' DOSE score ≥4	689 (22.9%)

3.1.2 Discussion

The study demonstrates that with the correct software support it is relatively simple to generate both a DOSE score and, the majority of the required coded co-morbidities from patient records and this approach could be replicated in Primary Care Practice with no clinician input time. The number of patients included in the study, whilst large for a research study, represents only 57% of the HHRA COPD patient population (excluding those who moved out of area) demonstrating that the 43% of patients, excluded from the study, are not having the basic QOF requirements recorded at an Annual Review over a 14 month period. Clearly there are a multitude of reasons why this might be, including, those too symptomatic from their lung disease (or other co-morbidities) to come into the GP surgery and those choosing not to take up the offer of a Primary Care Annual Review because they do not feel their COPD diagnosis impacts sufficiently on their life to choose to do so. Some of the information may also be recorded as free text which does not appear in the HHRA so may be missed. This percentage would be less concerning if the smoking rates and medication prescription rates in those excluded from the study were not so high,

suggesting that rather than data not being entered in coded manner, the Annual Review may not have happened in individuals likely to benefit, particularly with 8% requiring nebulised bronchodilators which suggests a significant symptom burden.

That the mortality rates are so much higher in those excluded from the study (13.7% vs 23.3% $p<0.001$) can be partly explained by the age spread of the two groups with 24.2% in those excluded from the study over 80 as opposed to 18.6% of those included. However, even if these patients with higher morbidity are too frail to come to the GP Practice or to perform spirometry, that they have not had the data recorded to generate an established DOSE score is concerning as MRC score, exacerbation rate and smoking status can all be established without face to face contact in a telephone review. This again indicates a group of patients vulnerable to having less contact with Primary Care clinicians despite significant morbidity.

Many of the comorbidity prevalence rates between those included and those excluded from the study are statistically significant, however in the main this probably simply reflects the large size of the study population rather than clinically relevant differences. There is a subtle increase in the prevalence of dementia, anxiety or depression and cerebrovascular disease in those excluded from the study group which may again reflect more vulnerable individuals, less able to engage with medical care due to their cognition or mental health status.

The co-existent diagnosis of asthma is common in around half of both groups. Whilst this could reflect true asthma/COPD overlap syndrome this is significantly over the rates of 15% and 20% of doctor diagnosed ACOS suggested in previous studies [1, 134]. These rates are more suggestive of diagnostic uncertainty, as is the rate of prescription of single agent inhaled corticosteroids which are not part of the GOLD guidance for treatment of COPD.

Once the low DOSE initial cohort was established, it would be expected that comorbidity rates would be higher in those with a high DOSE score and in the main our results reflect this. Presumably the high DOSE patients reflect a more symptomatic group of patients with either heavier smoking histories (and certainly higher current smoking rates at 62.0% compared to the 37.4% seen in the low DOSE initial cohort ($p <0.001$)) or greater genetic susceptibility to cigarette smoke in the lungs so may be more vulnerable to the effects of cigarette smoke in the vasculature [75]. Quite why rhinitis and sinus disease should be higher in the low DOSE initial cohort is unclear, but the rates are not vastly different (16.2% vs 12.7%) so the statistical significance of $p=0.005$ may reflect type 1 error rather than any clinical significance. The difference in the BMI distribution and incidence of pneumonia in the preceding two years between the groups supports

Jones et all in the use of a score of 4 as a cut off for a group at high risk of deterioration [56]. With significantly higher rates of pneumonia and a BMI <18 (and lower rates of BMI in the overweight and obese categories), those with a high DOSE score displaying well evidenced poor prognostic factors at baseline [63, 122, 148].

Of the outcomes allocating patients to the rapidly deteriorating subgroup, most individuals either experienced a hospital admission or deterioration into the high DOSE score group, both well evidenced as being associated with increasing subsequent mortality rates [56]. The low DOSE initial cohort was associated with 29.7% hospitalisation vs 64.7% in those with a high DOSE score and 12.3% vs 32.9% mortality over the subsequent four years. This is not dissimilar to the 11.0% (low DOSE) vs 42.4% (high DOSE) 5-year mortality rates demonstrated by Sundh et al which adds strength to the validity of our results [59]. The underlying disease severity in those patients with a high DOSE score may explain why 5-year mortality is considerably higher than that seen at four years in our study cohort.

During the study it became apparent that data extracts performed on the same patient population on different occasions, over the course of a year, generated marginally different numbers of patients (less than 20 individual patients in total). Further analysis of these individual patients by the data analyst working on the identifiable data (not available to the researchers) established a software error in the HHRA which would on occasion delete a patient entirely from the database if they died between the occasions the data extractions were performed. The software error has been resolved going forward so will not exist for studies using more current data in the database but our data will contain these small inaccuracies. The mortality rates seen in our study cohort of 12.3% and 32.9% in the low and high DOSE groups respectively are comparable with the rates seen by Sundh and Jones [56, 59]. This combined with the small numbers of patients potentially lost and the magnitude of the patient cohort lead us to believe that whilst our study may very slightly underestimate mortality, any error in the mortality numbers will be very small and unlikely to affect the validity of our results.

3.2 Certain Primary Care coded clinical, social and demographic characteristics are associated with the more rapidly deteriorating subgroup.

3.2.1 Results

Those patients who went on to experience an outcome that allocated them to the rapidly deteriorating subgroup had slightly higher rates of all comorbid diagnoses and total number of co-morbidities (2.0 vs 3.0 with 95% CI of 2.0 in both groups p <0.001) as shown in Table 3-7. The exception to this was in the case of rhinitis/sinus disease (18.0% vs 13.9%, p <0.001). The association between the cardiovascular co-morbidities, chronic kidney disease and anxiety or depression was significantly stronger in the rapidly deteriorating subgroup (ischaemic heart disease 23.9% vs 16.2% p <0.001, heart failure 8.1% vs 3.7% p <0.001, hypertension 47.1 vs 42% p <0.001, cerebrovascular disease 12.1% vs 6.6% p <0.001, peripheral vascular disease 7.4% vs 4.2% p <0.001, chronic kidney disease 21.1% vs 12.4% p <0.001 and anxiety or depression 37.2% vs 33.3% p =0.001). The incidence of pneumonia in the preceding two years was significantly higher in the rapidly deteriorating subgroup (24.9% vs 4.7% p<0.001) as was the likelihood of peripheral eosinophilia (49.5% vs 38.6% p<0.001). Allocation to the rapidly deteriorating subgroup was more strongly associated with increasing age (p <0.001) and the underweight BMI category (<18) (3.3% vs 1.5%, p <0.001). The overweight (25-29) and obese (30-34) category of BMI was less common in those in the rapidly deteriorating subgroup. The combination of all nebulised or inhaled bronchodilators, single agent or in combination with ICS were significantly associated with the more rapidly deteriorating subgroup.

Table 3-7 Associations between clinical characteristics and the rapidly deteriorating subgroup.

Table presenting the results of a bivariate analysis; the associations of each clinical characteristic with the rapidly deteriorating subgroup.

Clinical characteristics at baseline*	Individuals allocated to the rapidly deteriorating subgroup N=3007		Individuals allocated to the slowly deteriorating subgroup N=3883		Odds ratio (with 95% CI)	p value**
	N	Median (IQR)	N	Median (IQR)		
Gender					0.98 (0.89, 1.08)	0.668
Female	1370 (45.6%)		1749 (45.0%)			
Male	1637 (54.4%)		2134 (55.0%)			
Age group						
<50	59 (2.0%)		148 (3.8%)		1.00	
50-59	261 (8.7%)		533 (13.7%)		1.23 (0.88, 1.72)	0.230
60-69	813 (27.0%)		1348 (34.7%)		1.51 (1.11, 2.07)	0.010
70-79	1124 (37.4%)		1330 (34.3%)		2.12 (1.55, 2.90)	<0.001
80-89	679 (22.6%)		498 (12.8%)		3.42 (2.48, 4.72)	<0.001
90+	71 (2.4%)		26 (0.7%)		6.85 (3.99, 11.77)	<0.001
Deprivation decile (10 is most deprived)		6.0 (5.0)		7.0 (5.0)		<0.001
BMI						
<18	72 (3.3%)		42 (1.5%)		1.79 (1.21, 2.65)	0.004
18 to 24	758 (34.2%)		790 (28.3%)		1.00	
25 to 29	732 (33.1%)		1042 (37.3%)		0.73 (0.64, 0.84)	<0.001
30 to 34	409 (18.5%)		630 (22.6%)		0.68 (0.58, 0.79)	<0.001
>35	243 (11.0%)		288 (10.3%)		0.88 (0.72, 1.07)	0.202
History of pneumonia	750 (24.9%)		184 (4.7%)		6.68 (5.64, 7.91)	<0.001
Number of comorbidities		3.0 (2.0)		2.0 (2.0)		<0.001
Blood eosinophils ≥2%	1489 (49.5%)		1497 (38.6%)		1.56 (1.42, 1.72)	<0.001
History of Pulmonary Fibrosis	58 (1.9%)		45 (1.2%)		1.68 (1.13, 2.48)	0.010
History of Asthma	1543 (51.3%)		1955 (50.3%)		1.04 (0.94, 1.14)	0.426
History of Ischaemic Heart Disease	719 (23.9%)		629 (16.2%)		1.63 (1.44, 1.83)	<0.001
History of Heart Failure	244 (8.1%)		143 (3.7%)		2.31 (1.87, 2.86)	<0.001
History of Cor Pulmonale	11 (0.4%)		5 (0.1%)		2.85 (0.99, 8.20)	0.053
History of Hypertension	1416 (47.1%)		1629 (42.0%)		1.23 (1.12, 1.36)	<0.001

Clinical characteristics at baseline*	Individuals allocated to the rapidly deteriorating subgroup N=3007 N Median (IQR)	Individuals allocated to the slowly deteriorating subgroup N=3883 N Median (IQR)	Odds ratio (with 95% CI)	p value**
History of Hyperlipidaemia	583 (19.4%)	727 (18.7%)	1.04 (0.92, 1.18)	0.485
History of Osteoporosis	217 (7.2%)	191 (4.9%)	1.50 (1.23, 1.84)	<0.001
History of Cerebrovascular Disease	364 (12.1%)	255 (6.6%)	1.96 (1.66, 2.32)	<0.001
History of Dementia	59 (2.0%)	31 (0.8%)	2.49 (1.61, 3.85)	<0.001
History of Gastro Oesophageal Reflux	359 (11.9%)	398 (10.2%)	1.19 (1.02, 1.38)	0.026
History of Peripheral Vascular Disease	223 (7.4%)	164 (4.2%)	1.82 (1.48, 2.24)	<0.001
History of Connective Tissue Disease	87 (2.9%)	85 (2.2%)	1.33 (0.98, 1.80)	0.064
History of Anxiety Or Depression	1120 (37.2%)	1292 (33.3%)	1.19 (1.08, 1.31)	0.001
History of Lung Cancer	25 (0.8%)	20 (0.5%)	1.62 (0.90, 2.92)	0.109
History of Chronic Kidney Disease	633 (21.1%)	482 (12.4%)	1.88 (1.65, 2.14)	<0.001
History of Obstructive Sleep Apnoea	27 (0.9%)	28 (0.7%)	1.25 (0.73, 2.12)	0.414
History of Rhinitis/Sinus disease	418 (13.9%)	698 (18.0%)	0.74 (0.65, 0.84)	<0.001
History of Bronchiectasis	134 (4.5%)	132 (3.4%)	1.33 (1.04, 1.69)	0.024
History of Diabetes	472 (15.7%)	501 (12.9%)	1.26 (1.10, 1.44)	0.001
Prescriptions in the preceding twelve months:				
Nebulised bronchodilator	231 (7.7%)	101 (2.6%)	3.12 (2.45, 3.96)	<0.001
Single Agent ICS	907 (30.2%)	1103 (28.4%)	1.09 (0.98, 1.21)	0.112
ICS/LABA combination inhaler	1282 (42.6%)	1313 (33.8%)	1.45 (1.32, 1.60)	<0.001
Inhaled LABA or LAMA	1292 (43.0%)	1102 (28.4%)	1.90 (1.72, 2.10)	<0.001
Inhaled SAMA	713 (23.7%)	646 (16.6%)	1.56 (1.38, 1.75)	<0.001
Inhaled SABA	2371 (78.8%)	2719 (70.0%)	1.60 (1.43, 1.78)	<0.001

Key for Table 3-7

**All individuals: complete case data for all clinical characteristics with the exception of MRC score (98.5%), FEV1 percentage predicted (96.8%), smoking status (95.8%), Deprivation decile (missing data for one individual) and BMI (72.4%)*

***p values calculated using Chi squared test for categorical variables and Mann-Whitney test for continuous variables not normally distributed (comorbidity number and deprivation decile). Odds ratios presented for the categorical variables.*

3.2.2 Discussion

That eosinophilia is statistically significantly associated with the rapidly deteriorating subgroup, asthma is not associated with the rapidly deteriorating subgroup and rhinitis or sinus disease appear to be protective factors is interesting. One might expect similar associations between these three comorbidities and the rapidly deteriorating subgroup given their clinical association. We could postulate that this may be to do with the rates and accuracy of diagnoses of these conditions. A diagnosis of asthma was historically often given when patients developed symptoms of breathlessness, cough or wheeze in later years. Such nihilism existed around a diagnosis of COPD, it is conceivable that doctors may have labelled patients as asthmatic rather than deliver a diagnosis of a disease perceived as hopeless and without treatment options. Consequently, the diagnosis of asthma frequently appears on patients' historical records without good supporting clinical evidence. Conversely, the diagnosis of rhinitis or sinus disease exists very commonly across the population and patients will often only mention it if specifically questioned or if the symptoms are particularly severe. As such it may only be those most likely to have upper airways disease with prescribed treatment (motivated either by the clinician or patient) have a recorded diagnosis. This would suggest asthma may be over-recorded as a co-morbidity, lessening its significance and upper airways disease may be under-reported with a more vulnerable, untreated airway group existing but not diagnosed. This theory is supported by the positive association between a raised eosinophil count (a strong clinical indicator of atopy) and the rapidly deteriorating subgroup [69, 71].

The association between the cardiovascular co-morbidities and the rapidly deteriorating subgroup in COPD is not surprising given their common aetiology and existing evidence demonstrating these individuals have double the risk of COPD-related hospitalisation and increasing mortality post hospital discharge [63, 76-78]. Similarly, we would expect anxiety or depression to be associated with the rapidly deteriorating subgroup due to poorer access to health care due to lack of motivation, under-recognition of symptoms and higher smoking rates [98, 101, 103]. In both peripheral vascular disease and in the mood disorders patients may well struggle to stay active, either due to poor mobility or motivation, both co-morbidities are common reasons patients are unable to access Pulmonary Rehabilitation with all the clinical and social benefits it offers.

Our results demonstrating a strong association between the rapidly deteriorating subgroup and the underweight BMI category (<18) but a protective effect appears to be conferred from the

overweight (25-29) and obese (30-34) categories of BMI which is consistent with existing research [21, 63, 122]. The association between all bronchodilators (nebulised or inhaled) is slightly harder to explain. That the prescription of a nebulised bronchodilator in the preceding two years is associated with the rapidly deteriorating subgroup is unsurprising. The nebulised route of administration tends to be used either for those with very symptomatic disease or, may be used to avoid hospital admission and either of these possibilities are likely to be associated with the rapidly deteriorating subgroup. The increasing association with inhaled medication combinations which are used to treat manage COPD with more severe symptoms and airways obstruction suggests those in the rapidly deteriorating subgroup are more likely to present to a health professional and be prescribed inhalers of increasing potency.

The incidence of pneumonia in the preceding two years was significantly higher in the rapidly deteriorating subgroup (24.9% vs 4.7% p<0.001). Whilst there is good evidence for the poor prognostic effect of an episode of pneumonia in those with COPD, particularly in those already frail [147, 149], the magnitude of the association was striking and suggests that the poor prognostic significance of pneumonia may well be underestimated in clinical practice.

3.3 The development of a risk stratification model for early stage COPD, applicable in Primary Care, utilising Read code entries within patient records.

3.3.1 Results

Forward conditional logistic regression analysis was used to establish the combination of variables with the strongest association with the rapidly deteriorating subgroup with the results displayed in Table 3-8, demonstrating the combination of variables with the strongest prediction of allocation to the rapidly deteriorating subgroup. In this type of logistic regression analysis, the model effectively starts 'empty'. Variables are tested and added in the order that best improves the statistical significance of the model 'fit'. The model is complete once the addition of any further variable does not improve the fit to any statistically significant degree [200].

Those variables most strongly associated with allocation to the rapidly deteriorating subgroup, independently of the other variables in the model, include increasing age, BMI<18 compared to a BMI 18-24 (OR 1.61, 95%CI 1.05-2.48, p=0.029), a prescription of nebulised bronchodilators (OR 2.25, 95%CI 1.67-3.02, p <0.001), prescription of inhaled bronchodilators, in combination with ICS

(OR 1.27, 95%CI 1.11-1.45, p <0.001), or alone (OR 1.71, 95%CI 1.50-1.96, p <0.001) and a history of pneumonia (OR 5.12, 95%CI 4.19-6.27, p=<0.001). The magnitude of the association was partially striking for pneumonia with a five-fold increase in the odds of allocation to the rapidly deteriorating subgroup in keeping with the association seen in Table 3-7.

A BMI of above 25, when compared with the reference range (18-24) was independently associated with a reduction in the risk of allocation to the rapidly deteriorating subgroup (OR 0.75, 95%CI 0.64-0.87, p<0.001 and OR 0.67, 95%CI 0.56-0.80, p=<0.001 for overweight (25-29) and obese (30-34) respectively) as was a diagnosis of rhinitis/sinus disease (OR 0.76, 95%CI 0.64-0.89, p=0.001).

Table 3-8 Logistic regression model of clinical characteristics and prediction of allocation to the rapidly deteriorating subgroup.

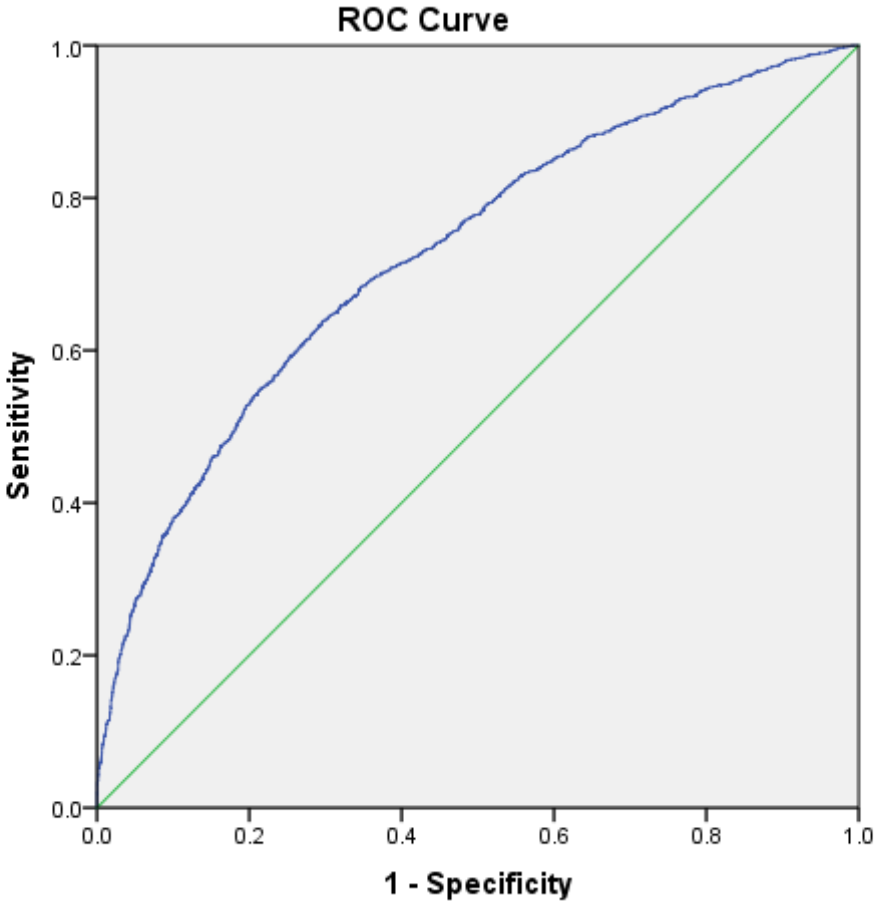
Logistic regression model demonstrating the association between clinical characteristics at study baseline (1st January 2010) and the odds of allocation to the rapidly deteriorating subgroup over the subsequent four years.

Clinical characteristic at baseline (N=5006)*	Odds Ratio (95% Confidence Interval)	p value
Age: <50 (reference)		
50-59	1.27 (0.82-1.96)	0.279
60-69	1.52 (1.01-2.29)	0.043
70-79	2.00 (1.33-3.00)	0.001
80-89	2.70 (1.76-4.14)	<0.001
90+	5.21 (2.58-10.53)	<0.001
Deprivation decile (association with decreasing deprivation)	0.95 (0.93-0.97)	<0.001
BMI: 18-24 (reference)		
<18	1.61 (1.05-2.48)	0.029
25-29	0.75 (0.64-0.87)	<0.001
30-34	0.67 (0.56-0.80)	<0.001
35+	0.87 (0.70-1.08)	0.197
History of pneumonia	5.12 (4.19-6.27)	<0.001
History of raised eosinophils (≥2%)	1.18 (1.04-1.34)	0.013
History of Heart Failure	1.44 (1.11-1.87)	0.007
History of Cerebrovascular Disease	1.49 (1.20-1.84)	<0.001
History of Peripheral Vascular Disease	1.53 (1.18-1.97)	0.001
History of Anxiety Or Depression	1.12 (1.05-1.36)	0.007
History of Chronic Kidney Disease	1.25 (1.06-1.48)	0.009
History of Rhinosinusitis	0.76 (0.64-0.89)	0.001
Prescriptions in preceding 12 months: Nebulised bronchodilator	2.25 (1.67-3.02)	<0.001
ICS/LABA combination inhaler	1.27 (1.11-1.45)	<0.001
Inhaled single agent LABA or LAMA	1.71 (1.50-1.96)	<0.001
Inhaled SAMA	1.43 (1.23-1.68)	<0.001
Inhaled SABA	1.24 (1.07-1.44)	0.004
Constant 0.275		

**excluded variables from model: gender, ischaemic heart disease, hypertension, osteoporosis, gastro-oesophageal reflux, diabetes, total number of comorbidities*

The model has a statistically significant ability to correctly allocate an individual to the rapidly deteriorating subgroup as assessed in the ROC curve analysis (**Error! Not a valid bookmark self-reference.**). A ROC curve analysis is used to demonstrate the predictive performance of the model i.e., how likely a model is to allocate an individual to the correct group. An area under the curve of 1 would indicate a model with 100% specificity and sensitivity whilst an area under the curve of 0.5 would indicate a model with 50% specificity and sensitivity (i.e., no better than chance). Our model demonstrated an area under the curve of 0.727 with narrow confidence intervals all significantly above 0.5 (95%CI 0.713-0.741, p<0.001) suggesting it has a reasonable ability to correctly allocate an individual to the rapidly deteriorating subgroup.

Figure 3-2 ROC Curve analysis for logistic regression model of clinical characteristics and prediction of allocation to the rapidly deteriorating subgroup.



3.3.2 Discussion

The logistic regression analysis highlights a combination of variables (all identified as independently associated in the bivariate analysis) associated with allocation of a patient to the

rapidly deteriorating subgroup. Encouragingly most of these are active, modifiable diseases, and have recommended disease optimisation pathways are already in place which could act as a template for focusing a holistic medical review.

The predictive performance of the model as demonstrated by the area under the curve of 0.727 is comparable with other models of prognostication in COPD as seen in Figure 3.3. It is important to note that these models all use mortality as their prognostic endpoint and, as our study used a variety of end points these are not direct comparators but does illustrate that model has an acceptable level of predictive performance.

Figure 3-3 Comparison of Area Under the Curve in our model and similar prognostic indices.

Prognostic Index	AUC	SE	95% CI	AUC	SE	95% CI
	Test Cohort			Validation Cohort		
Our Model	0.727	0.007	0.713-0.741			
ADO	0.675	0.010	0.655-0.694	0.568	0.014	0.541- 0.595
BODEx	0.483	0.015	0.453- 0.512	0.413	0.017	0.379- 0.447
DOSE	0.591	0.012	0.568- 0.614	0.515	0.015	0.485- 0.546
BARC	0.781	0.009	0.764- 0.792	0.695	0.012	0.695- 0.719

**Adapted from Bloom et al [188]*

Clearly, increasing age will always have one of the strongest associations with any health outcome which includes mortality and so, in this case, allocation to the rapidly deteriorating subgroup. Age is not a particularly helpful variable in a context where the aim is to highlight those variables which could be modified.

This model highlights a considerable number of variables associated with allocation to the rapidly deteriorating subgroup. To develop a model with clinical utility for health professionals with limited time resource, further development and investigation would be needed, aiming to produce a more concise model such as the example postulated in

Figure 3-4. In this example, as a reasonable starting point, non-modifiable risk factors such as age were removed and the model was focused on those risk factors (identified from the researchers' clinical experience) which seemed to provide the most relevant treatment pathways to be

addressed at a Primary Care Annual Review (e.g. ensuring an individual with a recent history of pneumonia had completed Pulmonary Rehabilitation and using blood eosinophilia as a surrogate marker for airways inflammation likely to respond to inhaled steroids, see section 2.4.3 for more detail of how these were chosen). This is the type of model, which could serve as a template for a yearly clinical review in day to day practice as it would be swift to administer with an intrinsic management strategy to guide clinicians in a proactive approach.

Figure 3-4 Potential model for predicting which patients with a low DOSE score are at risk of deterioration into the rapidly deteriorating subgroup.

Example of a risk prediction model with potential clinical utility for use in Primary Care.

Clinical Characteristic	Odds Ratio (95% Confidence Interval)	p value
Deprivation decile (associated with decreasing deprivation)	0.958	<0.001
BMI 18-24 (reference)		<0.001
BMI <18	1.622	0.022
BMI 25-29	0.759	<0.001
BMI 30-34	0.656	<0.001
BMI ≥ 35	0.839	0.099
History of pneumonia	5.968	<0.001
Blood eosinophils >2%	1.327	<0.001
History of Anxiety Or Depression	1.12	0.073
Prescription of Nebulised bronchodilators	2.702	<0.001
Constant 0.804		

3.4 General Discussion

The rationale behind this study was to ascertain whether a group of COPD patients, vulnerable to deterioration, could be identified using the data currently available in real world patient records. Identifying these patients would provide a subsequent opportunity to investigate if addressing their risk factors and optimising their care, could alter their disease progression and consequent clinical outcomes.

Previous research around the associations between co-morbidity and COPD has predominantly used databases representing research patient cohorts. Research cohorts provide data recorded at a level of accuracy, uniformity and detail which is unachievable in the normal run of patient care where patient records receive information from many sources [190]. The HHRA has the advantage of allowing us to develop a database study and a software approach in a very large patient population that encompasses all the data recoding anomalies present in real patient records. This allows us to establish if previous research can be utilised at real-world level. As with all real-world patient records, there will be some inaccuracies of diagnosis within this population and some COPD patients unidentified. This reflects the real-world nature of patient records and hence we used complete case analysis throughout rather than any imputation techniques to replace any missing data. Given the population size contained within Hampshire Health Record we do not feel missing data has had any statistically significant effect on the analysis.

Whilst one of the advantages of such a large data set is that it contains records from enough individuals to reflect the disparities in different clinicians' methods of data recording that make any research produced using it likely to be applicable to real world data, one of the disadvantages is the high likelihood of a degree of type 1 error in the results generated. Where the results are descriptive in nature such as those presented in tables 3-1 to 3-4, this is less relevant. It is much more relevant in the bivariate analyses seen in table 3-7 where the small p values suggesting a high degree of statistical significance of the results should be interpreted with caution. The results undoubtably contain a significant degree of type 1 error due to the size of the dataset but taken in the context of previous research the results can reasonably be used to add weight to the associations seen in previous datasets.

The study has demonstrated pneumonia to be a very strongly associated with current poor health status, as defined by high DOSE score, and strongly predictive of future deterioration, with the association being more than twice as strong as with a BMI of <18 which is known to be one of the poorest prognostic factors in COPD [1]. The link between pneumonia and health deterioration in COPD is well evidenced [147, 148] and our results add validity to this, however the strength of the association in our results is particularly interesting. This could have clinical utility to increase efforts to ensure these patients have received their influenza and pneumococcal vaccinations and that they have completed Pulmonary Rehabilitation once recovered from their infection. It could also be used as a warning flag to consider conversations and documentation around patient's wishes and needs when preparing for the end of life.

The negative associations of a BMI in the underweight category is to be expected, but the protective effects of a BMI in the overweight or obese group is equally interesting and supports developing evidence in this area [124]. It is particularly relevant when considering modifiable risk factors and optimisation of disease management, as care must be taken that appropriate advice and dietary support is given to patients with COPD where their needs are clearly different to that of the general population [122]. Further investigation is needed into whether this risk is entirely linked to the absolute BMI category the patient falls into or whether it can be altered by weight loss or weight gain.

The association between asthma and serum eosinophilia is well understood and COPD patients with raised serum eosinophils may represent patients with either an Asthma/COPD crossover diagnosis (known to have increased morbidity) or possibly a missed pure asthma diagnosis [134]. Equally this could be a surrogate marker of eosinophilic airways inflammation which, when optimised with inhaled steroids, has been shown to reduced exacerbation frequency [69].

The risk prediction model developed shows a reasonable predictive performance when compared to other similar prognostic indices, however it contains some non-modifiable variables which do not lend themselves to an intrinsic management plan. The natural development of this study would be to establish whether optimising those modifiable risk factors identified in the logistic regression model in Table 3-8 can modify these patients' future health status. Although strong evidence does not necessarily exist that optimisation of any of these comorbidities leads to better COPD health outcomes there are certainly suggestions that this is likely to be the case. We know that optimal control of asthma reduces asthma deaths [134] and if raised eosinophil levels are a clinical marker for eosinophilic asthma or ACOS, then treatment optimisation is likely to cause a clinical improvement. Similarly, the evidence that bisoprolol appears to improve mortality rates in COPD, independent of the presence of overt cardiac disease [83, 84], lends weight to the concept that optimisation of comorbidities may improve general patient health outcomes. If the model were refined and validated it could prove an exceptional clinical risk assessment tool suggesting an inherent management plan to be delivered on clinical review.

Finally, it would not be unreasonable to suggest that by using coded comorbidities rather than real time clinical patient assessment, the associations between these and poor health outcomes may be influenced by how and why different diagnoses may be recorded in the patient record rather than pure clinical associations. In the current coding scheme (TRUD) there are many ways to code different diagnoses, some of which are easier to locate in the coding scheme than others. It may be that those diagnoses which are harder to locate in the coding database are less

commonly used and thus under-represented in our data. Similarly, there are financial and administrational incentives to recording other co-morbidities. In addition to this, certain comorbidities cannot be separated by code e.g. anxiety and depression, as so many of the coding terms utilise both diagnoses. Whilst this will certainly influence our results, our study found most clinical characteristic prevalence rates were in keeping with those reported previously in the literature suggesting that this influence is not overwhelming. In addition, whilst being unable to separate anxiety from depression may lessen the association between one of the diagnoses with poor outcomes, this could be investigated further whilst validating the model in clinical cohorts. The management of both diagnoses follow similar pathways in Primary care which could be altered to suit the vulnerable individual upon review.

Data collection and recording and its consequent accuracy remains a challenge in the working NHS. We feel this utility of coded comorbidities in a real world population database should be considered the main strength of the study as it effectively provides a first validation of any model allowing us to move forward to create a validated clinical model which can be directly tested across different healthcare clinical databases to identify vulnerable individuals with the requirement of minimal administrational input.

3.5 Conclusions

A real world COPD patient population can be categorised by DOSE score into high or low scoring cohorts using data already available in Primary Care records. A patient cohort can be identified within a low risk DOSE cohort, who are at increased risk of allocation to a rapidly deteriorating subgroup, using their previously recorded clinical characteristics.

The prevalence of all clinical co-morbidities were higher in the rapidly deteriorating subgroup but the co-morbidities most strongly associated in isolation were an episode of pneumonia in the preceding two years and the presence of an eosinophil count of >2% of total white cell count in the preceding year. Logistic regression modelling can further develop this risk, demonstrating combinations of variables the most strongly associated with the rapidly deteriorating subgroup.

Identifying these patients provides the opportunity for investigation as to whether modification of these variables and COPD management optimisation can alter their disease progression and consequent clinical outcomes. Developing those modifiable elements of the logistic regression

analysis further into a risk stratification model lends itself for use identifying and managing vulnerable patients in Primary Care.

4 CLINICAL STUDY: Improving Health Outcomes in COPD: Methodology

4.1 Introduction

Within a population of symptomatic COPD patients deemed 'low risk' by DOSE score, this study aimed to establish whether our intervention of a prospective, medical assessment and individualised optimisation of care would alter respiratory health status and clinical outcomes at twelve months, when compared with standard care. The study was initially designed, carried out, and analysed as a cluster randomised, controlled effectiveness study using GP practices as clusters in a cohort-based analysis. During the course of the write up and the degree viva it became clear the study design was significantly flawed. It was felt by both the examiners and the candidate that the study still provided useful and original evidence and, as such, has been rewritten and presented as a feasibility study.

4.2 Study Objectives

Primary Care Practices are being asked to manage increasingly complex respiratory patients. Studies have shown improved clinical outcomes in patients with complex disease following Speciality review in Primary Care [186, 187]. The aim of the study is to test the feasibility of conducting a randomised control trial examining whether Speciality Physician review in Primary Care could improve health outcomes in a low risk COPD population".

Our research question was "What is the feasibility of conducting a cohort based randomised control trial using a Speciality Physician Review, compared with standard care, to improve health outcomes for low risk COPD patients.

Feasibility Outcomes:

1. To assess the success of recruitment and retention of individuals in this cohort randomised study design.
2. To identify any barriers to implementation of an intervention comprising a prospective Specialist Physician medical review and individualised optimisation of care.
3. To assess the feasibility of collecting outcome data using the endpoints designed below:
    - Change COPD symptoms defined by change in COPD Assessment Test (CAT) score at twelve months (Primary endpoint).

- Change in anxiety and depression levels at twelve months, as defined by 'The General Anxiety Disorder Assessment' (Appendix 6. GAD-7) and 'Patient Health Questionnaire' (Appendix 7. PHQ-9).
- Change in quality of life at twelve months, as defined by the EQ-5D and Health Thermometer, standardised instruments for use as measures of health outcome (Appendix 8. EQ5D and Health Thermometer).
- Exacerbation and hospitalisation rate at twelve months.
- Views of the study participants regarding the effect of the study on their health.

4.3 Ethical considerations

4.3.1 Ethics approval and research governance

The study was sponsored by the University of Southampton. For the purposes of ethical and research governance, the study underwent internal peer review in addition to the IRAS and University ERGO processes. The study design and protocol were reviewed by the study Patient Champion, an individual with chronic lung disease and extensive experience in lay input to research.

4.3.2 Confidentiality and data security

Patient identification and invitation to the study was conducted by the local Integrated COPD Team nurse and a GP Partner (at the preference of one Primary Care Practice), otherwise, all patient contact and review of Electronic Medical Records were conducted by the study Clinical Fellow (a Speciality Respiratory Physician), or by the study named Research Nurses. All Primary Care Practice patients were unknown to the study team unless they chose to respond to the invitation letter and expressed a wish to participate. Patient identifiable data for those expressing an interest in the study was accessible to the study Clinical Fellow, the Chief Investigator and the Study Nurses only. Whilst working in the Primary Care Practices, all study electronic data was stored on a password-protected research team laptop and all paper data was anonymised prior to transport back to the University of Southampton Hospitals Trust. All paperwork was stored in a locked filing cabinet in the Trust and all electronic data was stored on a restricted access Trust network.

4.3.3 Safety Reporting

An Adverse Event (AE) was defined any untoward and unexpected medical occurrence in a patient or clinical study subject who has been administered any research treatment or procedure, where there is a causal relationship with this treatment or procedure. A Serious Adverse Event (SAE) was defined as any untoward and unexpected medical occurrence where there is a causal relationship with the study, that:

- Results in death
- Is life-threatening.
- Requires hospitalisation or prolongation of existing inpatient hospitalisation.
- Results in persistent or significant disability or incapacity
- Is considered medically significant by Investigator.

All Serious Adverse Events and any unrelated deaths during the study period were recorded on the SAE reporting form and reported to the study Sponsor and REC.

Risks posed to the participants and adverse events were minimal given the study purpose and design of an altered mode of delivery of Standard Care. Unrelated deaths within the study group were expected given the relative age and frailty of the study group. The risks associated with performing spirometry were minimised by routine checks of recognised contraindications prior procedure. The only drug administered during the study was 400mcg Salbutamol where participants had not already taken a long-acting bronchodilator prior to spirometry. Allergic reactions and possible side of Salbutamol are rare, and any side effects were likely to swiftly subside.

Two serious adverse events occurred during the study. These took the form of two deaths occurring during the study period, one in each study arm. Both deaths were felt to be expected by the study team and relevant Primary Care Practice and of no relation to the study. They were reported to the University of Southampton and the Research Ethics Committee using the SAE reporting form and procedures. Both bodies were satisfied the deaths were unrelated to study participation.

4.4 Study Methodology

4.4.1 Primary Care Practice and Participant Recruitment

The process of Primary Care Practice and Participant recruitment is summarised in Figure 4-1.

Primary Care Practices from Southampton City Clinical Commissioning Group were recruited by direct email and telephone contact with the Practice Manager. Of ten practices contacted, all responded requesting further information and, after discussion with the study Clinical Fellow, six were keen to proceed. One Practice could not provide the room space required, one only wished to participate in studies undertaken by the Clinical Research Network in Wessex and two did not respond to further emails. These final two Practices were not re-contacted as the recruitment target of six Primary Care Practices had been met.

The Practices were randomly allocated to either the 'Intervention' or 'Control' arm by the study team, aiming to match primarily by size given the demographic profile, socio-economic status and rural/urban setting were comparable amongst the Practices which were all within a six mile radius in Southampton City. Following recruitment and randomisation, all practices were sent the study protocol and the Practice information letter.

All patients on the Practice COPD register with a DOSE score of <4 and a CAT score of >10 were eligible to become study participants. Potential participants were excluded only if they were unable to come to their Practice for review or were unable to consent to the study. Potentially eligible patients were identified by a local Integrated COPD team nurse or (in one Practice, due to Practice policy) a GP Partner using a manual data trawl of the Primary Care electronic record. A DOSE score was calculated for all individuals on the Practice COPD Registers and those patients with a DOSE score of <4 were invited by the Primary Care Practice to participate in a letter specific to either the control or intervention arm dependent on their Practice randomisation.

The DOSE score was calculated using the following approach:

1. **FEV_1:** The FEV_1 percentage of predicted values (European Coal and Steal Community equations) from the most recent spirometry data entry (all patients on the COPD register were included regardless of whether they had obstructive spirometry)
2. **mMRC score:** The closest chronological MRC score was converted to mMRC score which must fall within eighteen months of the FEV_1 measurement (if there was no FEV_1 measurement recorded, the most recent MRC score documented was used).

3. **Smoking status:** The closest chronological record of smoking status was used which must fall within eighteen months of the FEV_1 measurement (or MRC score if the FEV_1 measurement was absent).
4. **Exacerbations:** The number of COPD exacerbations recorded in the twelve months preceding the FEV_1 measurement (or MRC score if the FEV_1 measurement was absent).

   Exacerbation inclusion and exclusion criteria:

   a. An exacerbation was counted if a read code for 'exacerbation of COPD' or free text for exacerbation of COPD was recorded.
   b. An exacerbation was counted if antibiotics and/or steroids were prescribed for any respiratory tract illness or in combination with symptoms of cough, sputum, wheeze or dyspnoea.
   c. An exacerbation was counted if there was documentation of any respiratory tract infection or symptoms of acutely increased cough, sputum, wheeze or dyspnoea without the prescription of steroids or antibiotics.
   d. An exacerbation was counted if replacement antibiotic or steroid courses were issued for 'standby COPD medications' unless there was preceding text already detailing the exacerbation and notification of the standby medications being started.
   e. Three weeks were allowed between each exacerbation. Any additional exacerbation entry made in the three weeks post initial exacerbation was discounted.
5. Inclusion and exclusion criteria:
   a. If the DOSE score was ≥4 the patient was **excluded**
   b. If the FEV1 **AND** the MRC score were both missing the patient was **excluded**
   c. If the MRC score **AND** the smoking status were both missing the patient was **excluded**
   d. If there was incomplete data but, even with the missing data scoring in the top DOSE bracket, the patient would score less than four, the patient was **included**

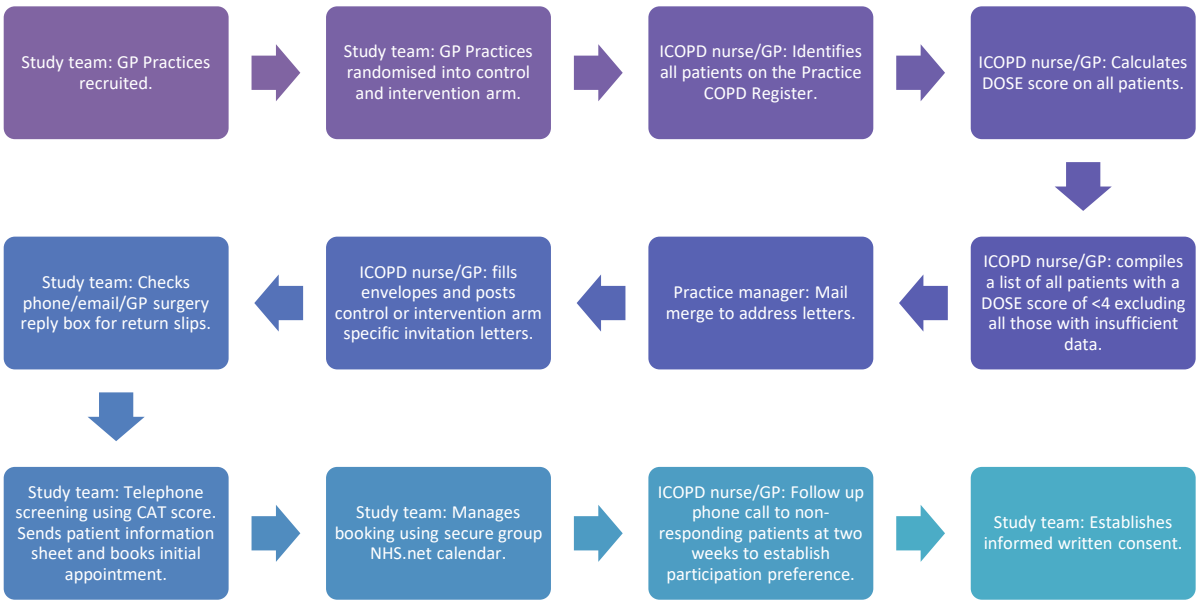
The COPD Integrated Care team or Practice GP provided a follow up phone call to non-responders two weeks after the initial contact by letter to establish their preference regarding study participation.

Individuals who wished to participate contacted the study team using the study email, study mobile phone or delivered a reply slip into a box situated at the reception desk of their Primary

Care Practice. These individuals were telephone screened by the study team to establish their CAT score. Those individuals responding to the Intervention arm letter were contacted and screened by the study Clinical Fellow (Respiratory Specialist Registrar). Those individuals responding to the Control arm letter were contacted and screened by one of the study Nurses. Those with a score of above 10 were invited to join the study and were sent the appropriate patient information leaflet (Appendix 9. Patient Information Leaflet: Intervention Arm and Appendix 10. Patient Information Leaflet: Control Arm). An appointment was arranged to take consent for participation into the study and perform the baseline visit a minimum of 48 hours after receiving the patient information. All appointments were administrated by the study team and managed using a secure NHS.net calendar.

Following written informed consent, the study initial assessment was carried out. If the participant wished to have more time to consider the information, an alternative date would have been arranged, however all participants declined this option. The consent process and all assessments took place at the participant's Primary Care Practice.

Figure 4-1 Summary of the participant recruitment process



4.4.2 Assessments; Control arm

At the initial appointment, after consent was established, participant reported clinical data was gathered by the Study Nurse, including exacerbation history, smoking status, mMRC score and co-morbidities. Post-bronchodilator spirometry was performed and the GAD-7, PHQ-9 and EQ-5D Index with Health Thermometer were self-administered with support by the Study Nurse. The participants were asked to keep an exacerbation diary for the next year, detailing antibiotics

and/or oral steroids requirement (Appendix 11. Exacerbation Diary). The initial appointment was allocated 1 hour which was felt to be sufficient time to gather this data and to also allow enough time after the appointment, to gather the same information as it was recorded in the participants' electronic medical record.

All patients with a diagnosis of COPD at randomisation (i.e. all patients) remained in the study regardless of whether airflow obstruction was seen on baseline spirometry. The study appointments did not replace participants' Annual Review with their Practice Nurse, but the practice was informed of QOF relevant information (spirometry, MRC score).

No alterations to usual treatment or recommendations were made by the research team to patients in the Control arm, with the exception of any disclosures felt to put the patient at imminent danger (e.g. suicidal intent or chest pain) in which case they were discussed with the duty GP who reviewed as necessary. If the participants had any queries, they were directed to the Practice Nurses or GPs as appropriate.

All participants were invited to attend for final review at twelve months. At ten months, an appointment was made with the participant by the study team for the twelve month review. A confirmatory letter was sent and telephone reminder made within a week of the appointment. During the final review, which was allocated 1 hour, post-bronchodilator spirometry was performed (forced manoeuvres only), any change in smoking status established and the exacerbation diary reviewed and correlated with Primary Care Electronic Medical Records in conjunction with the participant. The GAD, PHQ-9, EQ-5D, Health Thermometer and CAT scores were re-administered. The Study Nurse then performed a clinical review. Any needs identified and an action plan to optimise their respiratory health was shared with the participant's GP and Practice nurse. As in the initial appointment, all clinical information obtained was shared with the Primary Care practice.

4.4.3 Assessments; Intervention arm

At the initial appointment, in addition to the data gathered for the Control arm, a more detailed, personalised, medical review was conducted by the study Clinical Fellow (Respiratory Specialist Registrar). This was allocated an additional 30 minutes to the hour taken for the various assessments (as detailed in the description of the initial appointment for the Control arm) making the appointment 1 hour 30 minutes in total.

The structure of the detailed medical review is laid out in Appendix 12. Intervention Arm Initial Appointment Source Document. It consisted of a standard respiratory focussed history and examination and the development of a management plan assessing the need to address each of the areas listed below. The rationale behind each of these areas of the management plan was that they cover the GOLD guidance for the management of COPD in Primary Care. All the elements of this management plan would already be completed in a patient proactively and optimally managed at Primary Care level.

1. Diagnostic clarification
2. Referral to pulmonary rehabilitation
3. Dietary advice using the "Managing Malnutrition in COPD" red, yellow and green leaflets (www.malnutritionpathway.co.uk/copd)
4. Smoking cessation advice
5. Inhaler optimisation and technique assessment
6. Oxygen requirement
7. Mental Health onward referral
8. Unaddressed co-morbidity management plan
9. Social support
10. Further investigations suggested in the case of suspected undiagnosed disease.
11. Education around COPD
12. Onward referrals if appropriate

Education was provided for all participants with regards to the participants' respiratory diagnoses, identifying and treating exacerbations, inhaler technique, smoking cessation and nutrition. The Clinical Fellow suggested onward referral to other services in Primary or Secondary Care as required and these were suggested to the patients' GP but left to the GP's discretion to ensure they agreed with the plan and that the plan met with locally agreed treatment or referral guidelines. The exceptions to this were referrals to smoking cessation support or Pulmonary Rehabilitation which were made directly by the Clinical Fellow unless the GPs or Practice Nurses preferred to take responsibility for it themselves. Patients were also encouraged to self-refer to local mental health talking therapy services if this was felt to be appropriate. All clinical information obtained was shared in a timely manner with the Primary Care practice nominated GP and Practice Nurse.

A follow up appointment was booked during the initial appointment; to take place four to eight weeks later to follow up any clinical issues previously identified. This appointment lasted 20

minutes and reiterated the management plan, ensuring the patient understood the plan and that referrals, prescriptions and appointments had been made.

Over the study period, patients were consented to receive telephone or postal/email contact to ensure all clinical issues identified were being addressed as expected and all investigation results communicated in a timely fashion although this was rarely utilised (two patients only who struggled to access their prescriptions).

At twelve months all participants were invited for final review as per the Control arm.

4.4.4 Post-study follow up (all participants)

Following the final review all participants were invited to attend a free patient education session run by the study team as an expression of thanks (Appendix 13. Education Session Invite). The sessions were run at two locations to facilitate attendance from as many participants as possible. Those participants who attended were given a feedback form which they could opt either to fill in and return during the session or take away with them and return in a stamped, pre-addressed envelope. The form invited them to offer their opinions on the study design and the impact on their health (Appendix 14. Participant Feedback Form.). Those participants who chose not attend the education sessions were sent an anonymised feedback form to their home address with a stamped pre-addressed envelope to facilitate return to the study team.

4.4.5 Data cleaning and Analysis

Once all medical reviews were complete, all source document data was checked and uploaded into an Excel spreadsheet with the individuals identified only by their participant identifier. Data from ten participants from each study arm was verified against the source document and re-reviewed across all participant data at each time point to ensure transposition accuracy if any transposition errors were noted.

All data analyses were performed using SPSS statistics version 22.

A bivariate analysis was used to analyse the change in CAT score over the study period between the study groups. Initially this was performed as an intention to treat analysis; excluding only those lost to follow up. Subsequent bivariate analyses controlled for complicating factors such as Pulmonary Rehabilitation, alternative diagnoses or alternative sources of medical intervention. The same process was followed for analysis of the GAD-7, PHQ-9, EQ-5D and Health Thermometer data.

As is discussed in more detail in section 5.4.1, in hindsight, the analysis for this study was not conducted as for that of a cluster randomised analysis but rather that of an individual randomised study and no allowance was made for the effect of the clusters on the analysis. Whilst this was not appropriate in the context of a cluster randomised controlled trial, it is a reasonable approach in a feasibility study. In the case of this feasibility study the numbers were too small to draw any sort of conclusions regarding statistical significance so were presented simply as a comparison of percentages.

4.5 Statistical Considerations

4.5.1 The cluster randomised study design

A cluster randomised approach i.e. randomising Primary Care Practices rather than randomising individual patients was used as if was felt the presence of a respiratory-trained medical practitioner working within the Primary Care Practice and interacting with staff was likely to increase awareness of respiratory illness amongst the Practice staff. This could potentially alter 'usual care' in the Control arm, particularly so, if both arms occurred in a single practice. The cluster randomised approach reduced the possibility of this contamination. This advantages and limitations of the cluster randomised study design are discussed further in Section 5.4.1.

4.5.2 Sample size

The most recent systematic review of the CAT score as a clinical tool[39] has suggested further studies are needed to define a minimum clinically important difference but concluded it is likely to lie between 2 units[201] and 3.8 units[202]. An improvement of 2.9 units in CAT score was seen as an effect of Pulmonary Rehabilitation, currently recommended for patients with COPD by the National Institute for Clinical Excellence [203]. We took 2.9 units as our measure of clinical improvement, which required a minimum of 111 patients in each of the two arms to power the study to a significance of 80%.

Taking a conservative approach, we felt it would be prudent to allow for a 10% attrition in patient numbers over the study period. To allow for this we increased the intended sample sizes to between 73 and 124 patients per arm when using a clinical difference of 3.8 and 2.92 CAT points respectively. In hindsight, our approach to our study sample size was not appropriate for the cluster randomised controlled trial this was intended to be and this is discussed in more detail in section 5.4.1

5 CLINICAL STUDY: Improving Health Outcomes in COPD: Results and Discussion

Results will be discussed in terms of each of the feasibility outcomes:

1. To assess the success of recruitment and retention of individuals in this cohort randomised study design.
2. To identify any barriers to implementation of an intervention comprising a prospective Specialist Physician medical review and individualised optimisation of care.
3. To assess the feasibility of collecting outcome data using the endpoints designed below:
    - Change COPD symptoms defined by change in COPD Assessment Test (CAT) score at twelve months (primary endpoint).
    - Change in anxiety and depression levels at twelve months, as defined by 'The General Anxiety Disorder Assessment' and 'Patient Health Questionnaire'.
    - Change in quality of life at twelve months, as defined by the EQ-5D and Health Thermometer, standardised instruments for use as a measure of health outcome.
    - Exacerbation and hospitalisation rate at twelve months.
    - Views of the study participants regarding the effect of the study on their health.

5.1 The success of recruitment and retention of individuals in this cohort randomised study design

5.1.1 Results

A total of 120 participants were recruited from six Primary Care Practices. 76 participants were recruited from the Practices randomised to the Intervention arm and 44 in the Control arm Practices. The distribution of participants in the Intervention and Control arms are shown in Table 5-1 and Table 5-2. As is discussed further in 5.4.1 our sample size calculation was incorrect for a cluster randomised controlled trial but when discussing this in reference to the feasibility of the recruitment and retention strategy, we have discussed success in relation to the originally intended recruitment of between 73 and 124 participants to each study arm.

Overall the number of participants recruited fell below numbers needed to power the study as we had originally planned. Recruitment of 76 participants in the Intervention arm fell just below the 78 needed to power the study for a change in CAT score of 3.8 points. Recruitment of 44

participants in the Control arm was significantly below the 78 patients required. Our attrition rate was also slightly higher than the 10% anticipated at 15.9% in the Control arm and 11.8% in the Intervention arm.

5.1.2 Population description

Of the 120 participants, 104 (86.7%) were followed by primary measure (CAT score) to the study completion at twelve months, 67 (88.2%) in the Intervention arm and 37 (84.1%) in the Control arm. 16 participants (13.3%) were lost to follow up, 7 (15.9%) in the Control arm and 9 (11.8%) in the Intervention arm. One participant died in each arm and these are included in the figures for those lost to follow up.

Table 5-1 Distribution of participants within the Study Intervention arm

	Participants recruited	Participants followed to study completion	Moved GP Practice and included in follow up numbers	Moved GP Practice and NOT included in follow up numbers	Lost to follow up due to established poor health	Lost to follow up as did not respond to study contact	Death during the study period
GP Surgery 1- BH	17	13	0	0	0	4	0
GP Surgery 2- BL	32	30	1	0	1	0	1
GP Surgery 3- SL	27	24	0	1	0	3	0

Table 5-2 Distribution of participants within the Study Control arm

	Participants recruited	Participants followed to study completion	Moved GP Practice and included in follow up numbers	Moved GP Practice and NOT included in follow up numbers	Lost to follow up due to established poor health	Lost to follow up as did not respond to study contact	Death during the study period
GP Surgery 4- AD	17	13	0	0	3	1	1
GP Surgery 5- AM	15	15	1	0	0	0	0
GP Surgery 6- PS	12	10	1	0	1	1	0

The study population characteristics at baseline are displayed in

Table 5-3 and

Table 5-4. The populations were broadly similar as expected given the Primary Care Practices were all recruited from Southampton City Clinical Commissioning Group. The area has an inner city population with all Practices serving residential areas with significant poverty and deprivation levels. Our population had a median age of 70 in both cohorts with a median age of leaving education of 15. The Control arm were suggested to be slightly more vulnerable and frail with a higher percentage living alone (36.4% vs 26.3%), using a mobility aid (36.4% vs 27.6%) and requiring domestic help (20.5% vs 11.8%).

Both study populations had relatively similar COPD severity measures with moderate median airways obstruction (FEV1 percentage predicted of 65.0% in the Control arm and 66.5% in the Intervention arm), median exacerbation rates of 1.0 in the last twelve months and pack year histories of 36.5-37.5. The ongoing smoking rates were relatively high (18.2% in the Control arm vs 17.1% in the Intervention arm) as were the never smoker rates (11.4% in the Control arm vs 6.6% in the Intervention arm). Both study arms were relatively breathless and whilst the difference was non- significant, it was higher in the Control arm with 61.4% of the participants scoring 2-4 on the modified mMRC score compared with 48.6% of the Intervention arm. 93.2% of the Control arm and 80.3% of the Intervention arm participants had the diagnosis of COPD confirmed by study spirometry or clinical evaluation with the remainder having a different diagnosis felt to be responsible for their symptoms.

The study arms had similar rates of co-morbidities with slightly higher rates of most of the co-morbidities in the Intervention arm. Higher prevalence rates of hyperlipidaemia (31.8% vs 53.9%) and gastro-oesophageal reflux disease (29.5% vs 48.7%) were seen in the Intervention arm. The prevalence rates of osteoporosis were also higher (2.3% vs 14.5%). Relatively high rates of

participants were already under ongoing management by the local secondary care Respiratory Physicians (13.6% vs 14.5%).

P values have been included in

Table 5-3 and

Table 5-4 for ease of viewing as there is a considerable difference in the size of the Control and Intervention arm. This should be viewed as a guide only, as, given the small size of the groups it is not appropriate to draw robust conclusions of statistical significance.

Table 5-3 Table demonstrating the study population characteristics at baseline.

Variable	Control arm (N=44)	Intervention arm (N=76)	p

	N	Median, IQR, (range)	N	Median, IQR, (range)	value
Gender					0.877
male	26 (59.1%)		46 (60.5%)		
female	18 (40.9%)		30 (39.5%)		
Age**		70.2, 8.23		70.0, 9.82	0.891
BMI		28.3, 9.0 (20.2-43.9)		27.5, 6.9 (16-45)	0.357
Age left education		15, 1.8 (14-22)		15, 1.0 (8-21)	0.539
Lives alone	16 (36.4%)		20 (26.3%)		0.247
Uses mobility aid	16 (36.4%)		21 (27.6%)		0.318
Domestic help	9 (20.5%)		9 (11.8%)		0.203
Tobacco smoking status					0.633
Never smoker	5 (11.4%)		5 (6.6.%)		
Ex smoker	31 (70.5%)		58 (76.3%)		
Current smoker	8 (18.2%)		13 (17.1%)		
Pack year history		36.5, 38.8 (0-107)		37.5, 41.3 (0-120)	0.864
Cannabis smoking status					0.593
Never smoker	41 (93.2%)		72 (94.7%)		
Ex smoker	0 (0.0%)		1 (1.3%)		
Current smoker	3 (6.8%)		3 (3.9%)		
Crack cocaine smoking status					*0.601
Never smoker	43 (97.7%)		75 (98.7%)		
Ex smoker	1 (2.3%)		1 (1.3%)		
Current smoker	0 (0.0%)		0 (0.0%)		
Heroin smoking status					0.693
Never smoker	43 (97.7%)		74 (97.4%)		
Ex smoker	1 (2.3%)		1 (1.3%)		
Current smoker	0 (0.0%)		1 (1.3%)		
FEV_1 percentage of predicted		65.0, 17 (27-100)		66.5, 27 (38-131)	0.767
mMRC score					0.617
0	4 (9.1%)		10 (13.2%)		
1	13 (29.5%)		29 (38.2%)		
2	15 (34.1%)		21 (27.6%)		
3	8 (18.2%)		13 (17.1%)		
4	4 (9.1%)		3 (3.9%)		
Exacerbation rate in the previous year		1.0, 2.0 (0-4)		1.0, 2.0 (0-8)	0.448
Completed acute PR	14 (31.8%)		24 (31.6%)		0.978
Attending PR maintenance	6 (13.6%)		6 (7.9%)		*0.157
Attends Respiratory clinic at baseline	6 (13.6%)		11 (14.5%)		0.899

** Fisher's Exact Test used to calculate p value due to small group numbers*

***Normally distributed variables, reported using mean, standard deviation and p values calculated using T-test*

Table 5-4 Table demonstrating the study population comorbidities at baseline.

Variable	Control arm (N=44)	Intervention arm (N=76)	p value
Osteoporosis	1 (2.3%)	11 (14.5%)	*0.054
Dementia	0 (0.0%)	0 (0.0%)	
Pneumonia in preceding 2 years	1 (2.3%)	3 (3.9%)	*0.533
Rhinitis or sinus disease	6 (13.6%)	16 (21.1%)	0.312
Ischaemic heart disease	6 (13.6%)	10 (13.2%)	0.941
Left Ventricular Failure	1 (2.3%)	7 (9.2%)	*0.255
Right Ventricular Failure	0 (0.0%)	2 (2.6%)	*0.532
Asthma	15 (34.1%)	30 (39.5%)	0.557
Bronchiectasis	0 (0.0%)	1 (1.3%)	*0.633
Pulmonary Fibrosis	1 (2.3%)	3 (3.9%)	*0.533
Hypertension	25 (56.8%)	31 (40.8%)	0.090
Anxiety	10 (22.7%)	19 (25.0%)	0.779
Depression	14 (31.8%)	28 (36.8%)	0.578
Diabetes Mellitus	5 (11.4%)	15 (19.7%)	0.236
Hyperlipidaemia	14 (31.8%)	41 (53.9%)	0.019
Obstructive Sleep Apnoea	2 (4.5%)	2 (2.6%)	*0.623
Gastro-Oesophageal Reflux Disease	13 (29.5%)	37 (48.7%)	0.040
Confirmation of COPD diagnosis	41 (93.2%)	61 (80.3%)	0.056

** Fisher's Exact Test used to calculate p value due to small group numbers*

Table 5-5 and Figure 5-1 describe the distribution of the symptom scores as a whole and the individual components of the CAT score at baseline (See Appendix 15. Table showing baseline distribution of CAT score components between the Intervention and Control arms. for the table displaying the corresponding data). All symptom scores were slightly higher in the Intervention arm (or lower in the case of EQ5D), representing marginally worse symptom burden. The exception was the Health Thermometer where the marginally higher score in the Intervention arm represents a better subjective quality of health.

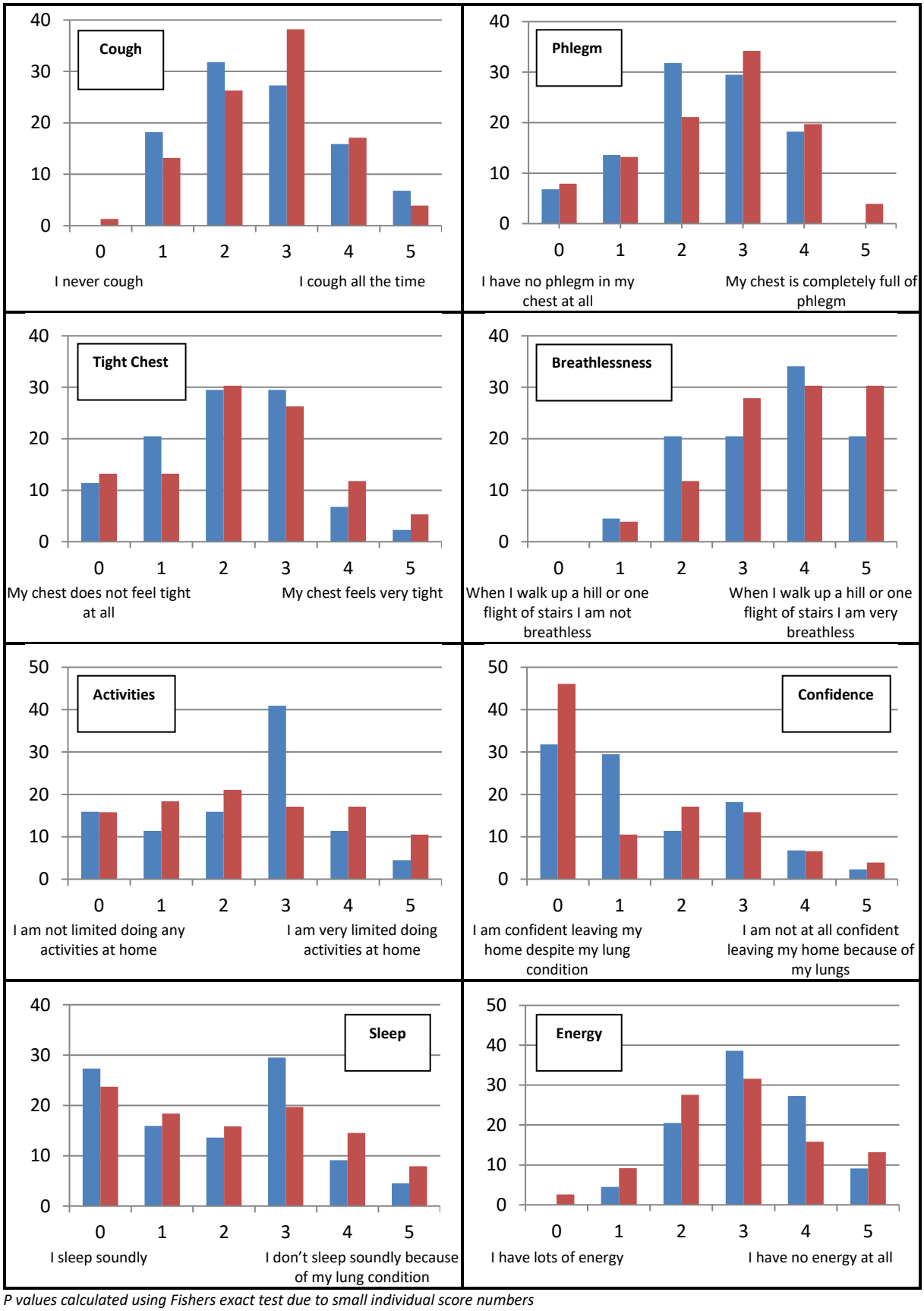
The individual breakdown of the CAT score suggested that the Intervention arm participants were marginally more symptomatic with the respiratory specific symptoms (breathlessness, cough, phlegm production and tight chest) whereas the Control arm participants struggled more with confidence and energy (Figure 5-1).

Table 5-5 **Table demonstrating the Study population COPD symptom scores at baseline.**

Symptom scores at Baseline	Control arm (N=44) Median, IQR, (range)	Intervention arm (N=76) Median, IQR, (range)
CAT score at baseline	18.5, 11.0, (11.0-30.0)	19.0, 10.0, (11.0-38.0)
PHQ-9 score at baseline	4.0, 8.0 (0.0-22.0)	6.0, 7.0 (0.0-23.0)
GAD-7 score at baseline	2.0, 8.0 (0.0-20.0)	4.0, 7.0 (0.0-20.0)
EQ5D score at baseline	0.717, 0.321 (-0.080-1.000)	0.664, 0.175, (-0.104-1.000)
Health thermometer score at baseline*	63.1, 19.5 (25-100)	66.7, 16.4 (25-98)

**Complete case data for all variables with the exception of health thermometer score, eight missing scores (93% data collection)*

Figure 5-1 Baseline distribution of CAT score components between the Intervention and Control arms



P values calculated using Fishers exact test due to small individual score numbers

Key for Figure 5-1 *Intervention arm* *Control arm*

5.1.3 Discussion

As discussed, the number of participants recruited fell below numbers needed to power the study as we had originally planned and our attrition rate was also slightly higher than the 10% anticipated at 15.9% in the Control arm and 11.8% in the Intervention arm.

One barrier to the recruitment strategy included the small study size and consequently only having a small number of clusters (six). This amplified the effect of differences in the size of the Primary Care Practices from which we recruited. After the Practices were matched for approximate size (the two largest, the two medium sized and the two smallest size) they were randomised using an IT randomisation programme. This happened to randomise the larger Practices to the intervention arm in the two pairings where the size difference was the most significant. Therefore, the smaller numbers recruited for the Control arm may partly relate to the small size of the Control Primary Care Practices which served a slightly smaller patient population, this would be likely to be less significant in a larger trial population with more clusters and could also be controlled for as part of a further developed randomisation strategy.

A second barrier to the recruitment strategy is likely to relate to the smaller amount of clinical input offered to those in the Control arm with the offer of a medical review being performed by a Respiratory Specialist nurse at the end of twelve months rather than the offer of three reviews performed by a Respiratory Physician. Many patients may not be aware of the added expertise offered by a Specialist Nurse when compared to the Practice Nurses and Nurse Practitioners they see on a regular basis at their Primary Care Practices and this may have compounded the perceived difference in input. Whether patients are recruited before or after their Primary Care Practice is randomised to an Intervention or Control arm could be considered going forward. This may lead to an overall slightly reduced recruitment but more equitable recruitment between the study arms.

A third barrier to the success of the recruitment strategy is the likelihood we introduced selection bias to the recruitment strategy by using a different person and job role to recruit to the intervention and control arm. This is discussed in more detail in section 5.4.1 and would need to be modified in a future study, allocating staff's recruitment involvement evenly across the study arms.

The study population represented the relatively symptomatic, vulnerable and co-morbid population one would expect to find in an inner city area with relatively high poverty and deprivation levels. The comorbidity rates were broadly similar with differences between the two

likely to be related to the small study numbers. There were higher frailty levels and vulnerability suggested in the Control arm by the higher use of mobility aids, domestic help and living alone. Whilst these differences were not likely to be significant and likely instead to be due to the small study numbers, this may have contributed to the relatively higher level of Control arm participants lost to follow up.

Overall, despite being low risk by DOSE score, these were still a comorbid, frail group of patients. Whilst this is not a surprise in a group of COPD patients it could well be amplified if deprivation levels were higher in a future recruitment population. This frailty is likely to represent more of a barrier to recruitment and retention than we had initially anticipated and would need to be accounted for in any future study recruitment strategy.

5.2 Implementation of an intervention comprising a prospective Specialist Physician medical review and individualised optimisation of care

5.2.1 Results

Following medical review at the initial and follow up appointments, the Clinical Fellow made recommendations to the participant and their Primary Care Practice in the case of 72 (94.7%) participants. These changes are detailed in Table 5-6. Most notably, 27 participants (35.5%) had a change in diagnosis with 15 (19.7%) not meeting the internationally recognised criteria for a diagnosis of COPD. 59 participants (77.6%) had a recommended change of inhaled medication and 19 (25%) participants were recommended a new non-inhaled medication (predominantly related to sputum thinning, gastro-oesophageal reflux disease or addressing symptoms of rhinitis and sinus disease). 21 (27.6%) participants were suitable for referral and happy to be referred to acute Pulmonary Rehabilitation Services and 3 (3.9%) participants were suitable for the local Pulmonary Rehabilitation maintenance classes.

16 participants (21.1%) were signposted to additional mental health treatment. This mainly took the form of supporting participants to self-refer to the local mental health talking therapies service ‘Steps to Wellbeing’. Three individuals were directed back to their GPs as their mental health problems were longstanding and required more specialised input. 4 individuals (5.3%) were referred to the Primary Care Practice ‘over 65’ Nurse Specialists or local Dementia Nurse Specialists for guidance regarding more social support for themselves or their relative or carer.

At twelve months, each participant in whom changes had been recommended were assessed as to whether these recommendations had been enacted. In 61 (84.7%) of the participants all changes had been enacted and in 10 participants (13.9%), not all the changes had been enacted so were marked 'partially enacted'. The management suggestions not enacted included, patients who had not accessed either Pulmonary Rehabilitation (in three cases as the GP felt they were too well and would not benefit, in two cases due to participant lack of engagement and in two cases due to the patient developing co-morbidities which precluded them) or Steps to Wellbeing (in two cases the participant contacted the service then declined to participate and in two cases they did not contact the service). One patient (1.4%) had none of their recommended changes (new inhaled medication) enacted as they had spent most of the year out of the country.

Table 5-6 Table demonstrating the interventions made at the initial study visit.

Intervention	Study Intervention Population N= 76
COPD Diagnosis removed	15 (19.7%)
New Diagnosis	27 (35.5%)
Change in Diagnosis	27 (35.5%)
Change in Inhaled Medication recommended	59 (77.6%)
New Medication (Non-Inhaled) recommended	19 (25%)
Referral to Oxygen Service	1 (1.3%)
Referral to Mental Health Service	16 (21.1%)
Referral for Social Intervention	4 (5.3%)
Referral to Pulmonary Rehabilitation (acute)	21 (27.6%)
Referral to Pulmonary Rehabilitation (maintenance)	3 (3.9%)
Intervention enacted at 12 months? (N=72)	
yes	61 (84.7%)
partially	10 (13.9%)
no	1 (1.4%)

5.2.2 Discussion

We had anticipated there would be documented diagnostic inaccuracy seen in the patient group as this is relatively common throughout both Primary and Secondary Care [190]. At nearly 20% this level was somewhat higher than we had initially expected but of a similar level to the 23.6% seen in the study by Gillett, Lippiett, Astles et al [187]. Interestingly, many of these individuals expressed doubt in their diagnosis and were not surprised to see a change. It may be that this slightly high level of diagnostic inaccuracy is disproportionate in the study population as these patients are less likely to have the true cause of their symptoms addressed thus may be more symptomatic and more likely to wish to participate in a study offering a medical review.

The change in inhaled medications ranged from removal of inhaled medications entirely to changing to a different inhaler device to introduction of inhalers with a new drug class. The bulk of the new drug class of inhalers involved introduction of long acting bronchodilators in single or combination devices. This is higher levels of inhaler change than seen in the Gillett, Lippiett & Astles study but this study had a different patient population consisting predominantly of asthma patients in whom there are not the variety of inhaled therapies and this is likely to reduce the potential number of inhaled medication changes made. All prescription changes were made by the GPs themselves. The informal feedback from the GPs was that they found this a rewarding and educational process which altered their prescribing choices. Many of them mentioned that they found the choice of inhalers overwhelming and tended to leave this choice to their Practice Nurses (including the drug classes contained in the inhaler as well as the device itself). They also expressed surprise at the difference they saw in the participants' symptoms with the introduction of a long acting bronchodilator as it was not something they had previously considered to have any real cost benefit.

The Pulmonary Rehabilitation referrals were enacted through the Practice Nurses in two Practices and through the GP in the other Practice. The Practice Nurses were particularly interested in the process and articulated that they found the process educational as it gave them confidence to refer patients they would not have otherwise have considered suitable.

An obvious barrier to this model at a larger scale or as a widespread model of care is the finite and expensive resource of Speciality Physicians and the time consuming nature of the intervention. This is discussed further in section 5.4.1.

Overall, there were no logistical or clinical barriers highlighted by our study to a Speciality Respiratory review in Primary Care. The review facilitated diagnostic clarity and changes in patient management well evidenced to improve health outcomes. Despite our best efforts we did not expect all the changes recommended to be enacted, particularly with regard to Pulmonary Rehabilitation and Steps to Wellbeing referrals as these have high patient dropout levels in the case of Pulmonary Rehabilitation and patients often find it challenging to self-refer to Mental Health Services. The drop-out rate for those who started Pulmonary Rehabilitation was encouragingly low with 12 out of 14 completing the course although by volunteering for a study the participants were like to be a highly self motivated subgroup of the general population.

Reviewing patients in the familiar surroundings of their Primary Care Practice was viewed positively by the study participants and informal feedback from the Practice staff was they found

it a positive and educational experience. A barrier to the feasibility of this study design is that this is difficult to quantify further as much of the feedback is informal and the patient feedback form was fairly simplistic. This could be developed to be a far more informative part of the study by using an additional qualitative element to further explore the views of the study participants (both Primary Care Practice staff and patients).

5.3 The feasibility of collecting outcome data using the defined endpoints

5.3.1 Results

As discussed in section **Error! Reference source not found.**, of the 120 study participants, 104 (86.7%) were followed by primary measure (CAT score) to the study completion at twelve months, 67 (88.2%) in the intervention arm and 37 (84.1%) in the control arm.

Table 5-7 shows the difference in CAT, PHQ-9, GAD-7, EQ5D and EQ5D Health Thermometer scores between the control and intervention arm at the study follow up appointment. At twelve months the primary outcome measure of CAT score (the greater the score the greater the symptoms burden) showed an improvement in score in both arms reflecting an improvement in COPD symptom burden across the whole study population, there was a slightly higher score in the Intervention arm than the Control arm (median score of 16 vs 14), but the change in CAT score did not suggest a difference between the study arms (median change of -3.9 vs -4.0).

The secondary outcomes of GAD-7 (anxiety measure) and PHQ-9 (depression measure) at twelve months showed small improvements in score in both study arms suggesting a mild improvement in anxiety and depression scores across the study population (the greater the scores the greater the anxiety or depression symptom burden). In the case of the GAD score at twelve months, the overall score was higher in the Intervention than the Control arm as was the case at baseline (median score of 2.0 vs 3.0). The change in GAD-7 score was negligible in both study arms (median change of 0.0 in both study arms).

The PHQ-9 overall score at twelve months was also higher in the Intervention than the Control arm as again was the case at baseline (median score of 3.0 vs 4.0). The change in PHQ-9 score was negligible in both study arms (median change of -1.0 vs 0.0).

The secondary EQ5D index value (the higher the score, the better the functional quality of life) showed improved scores from baseline in the intervention arm (in both overall score and change in score), whereas the index score in the Control arm was static (median index value 0.716 vs

0.735 and median change in index value -0.021vs 0.052). The Health Thermometer scores showed similar change, slightly improving in the Intervention arm (median Health Thermometer score 60.0 vs 70.0, median change in Health Thermometer score -0.6 vs 0.3).

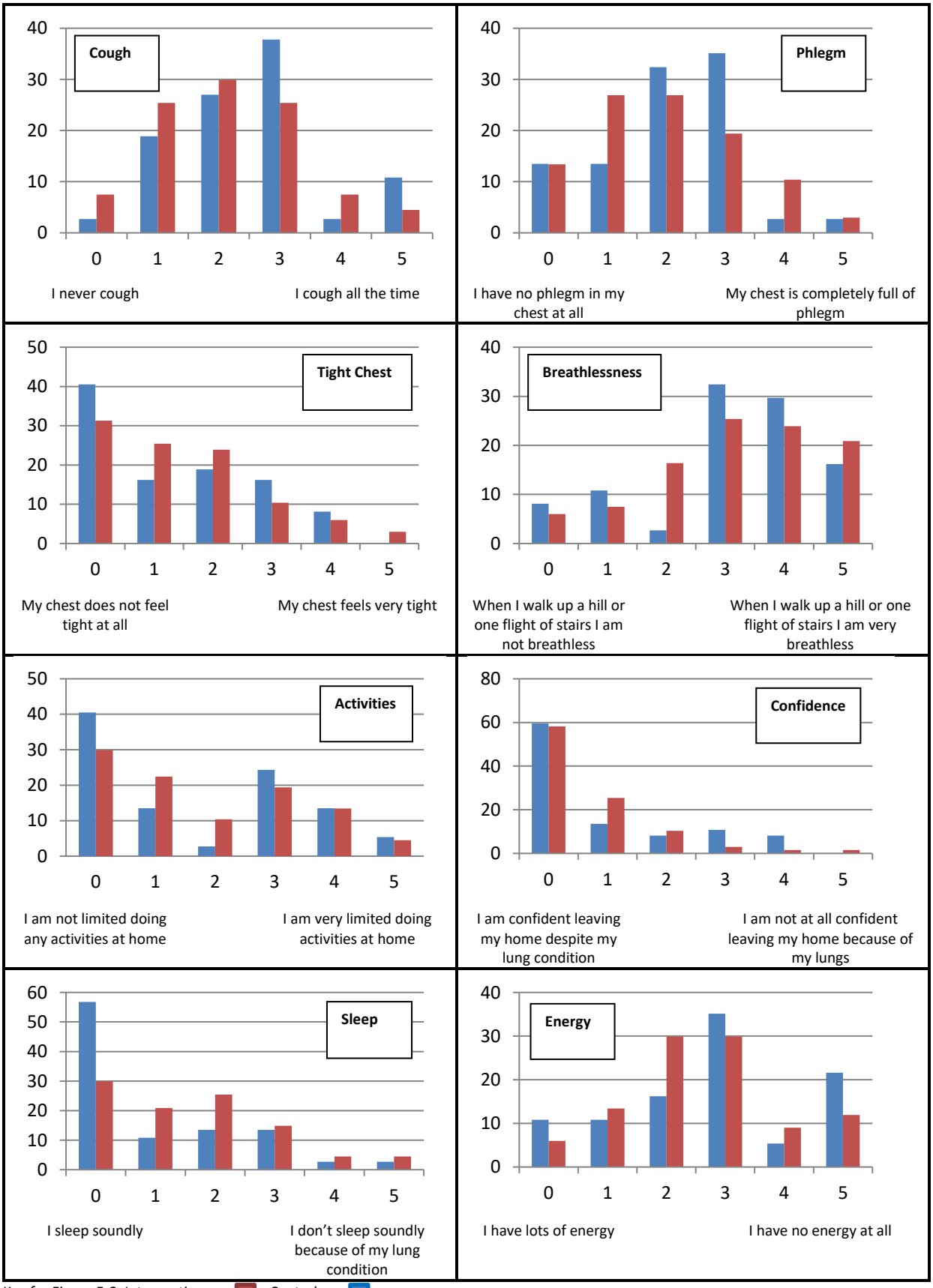
Table 5-7 Change in symptom scores at twelve month follow up.

Symptom score	N (% data collection)	Control arm (N=37)		Intervention arm (N=67)	
		N	Median, IQR, (range)	N	Median, IQR, (range)
CAT score at twelve month follow up	104 (100%)	37 (100%)	16.0, 10.0 (1.0-30.0)	67 (100%)	14.0, 11.0 (3.0-38.0)
Change in CAT score over the study period**	104 (100%)	37 (100%)	-3.9, 5.7 (-19.0-8.0)**	67 (100%)	-4.0, 5.8 (-20.0-10.0)**
GAD-7 score at twelve month follow up	104 (100%)	37 (100%)	2.0, 7.0 (0.0-20.0)	67 (100%)	3.0, 9.0 (0.0-20.0)
Change in GAD-7 score over the study period	104 (100%)	37 (100%)	0.0, 5.0 (-13.0-6.0)	67 (100%)	0.0, 5.0 (-9-16.0)
PHQ-9 score at twelve month follow up	104 (100%)	37 (100%)	3.0, 11.0 (0.0-21.0)	67 (100%)	4.0, 6.0 (0.0-24.0)
Change in PHQ-9 score over the study period	104 (100%)	37 (100%)	-1.0, 6.0 (-13.0-10.0)	67 (100%)	0.0, 5.0 (-21-6.0)
EQ5D index value at twelve month follow up	104 (100%)	37 (100%)	0.716, 0.275 (-0.429-1.000)	67 (100%)	0.735, 0.216 (0.159-1.000)
Change in EQ5D index value over the study period**	104 (100%)	37 (100%)	-0.021, 0.199 (-0.487-0.521)**	67 (100%)	0.052, 0.172 (-0.368-0.502)**
EQ5D health thermometer score at twelve month follow up	104 (100%)	37 (100%)	60.0, 28.0 (10.0-100.0)	67 (100%)	70.0, 30.0 (30.0-100.0)
Change in EQ5D health thermometer score over the study period**	104 (100%)	37 (100%)	-0.6, 20.9 (-40.0-40.0)**	67 (100%)	0.3, 15.5 (-50.0-35.0)**

**Complete case data for all variables.*
***Normally distributed variables, reported using mean, standard deviation*

The individual components of the CAT score are shown in Figure 5-2. None of the individual components suggested an obvious change over the study period. In contrast to the baseline scores, at twelve months, the Intervention arm represented the population with slightly less burden from the respiratory based symptoms of cough, tight chest, phlegm production and breathlessness with a suggestion of a small improvement in their confidence and sleep scores.

Figure 5-2 Distribution of CAT score components between the Intervention and Control arms at twelve months



Key for Figure 5-2 Intervention arm Control arm

As seen in **Error! Not a valid bookmark self-reference.** minimal change was seen in the change in CAT, PHQ-9, GAD-7, EQ5D and EQ5D Health Thermometer scores between the control and

intervention arm at twelve months when only those participants with study confirmed diagnosis of COPD were included. The results are only minimally changed from that of the whole cohort although the suggested association between the change in EQ5D index value and the clinical intervention becomes stronger.

Table 5-8 Change in symptom scores at twelve month follow up in those participants with confirmed COPD.

Symptom score	N (% data collection)	Control arm (N=34)		Intervention arm (N=53)	
		N	Median, IQR, (range)	N	Median, IQR, (range)
Change in CAT score over the study period**	87 (100%)	34 (100.0%)	-4.3, 5.9 (-19.0-8.0)	53 (100%)	-4.4, 5.8 (-20.0-8.0)
Change in GAD-7 score over the study period	87(100%)	34 (100.0%)	0.0, 5.0 (-13.0-6.0)	53 (100.0%)	0.0, 5.0 (-9.0-12.0)
Change in PHQ-9 score over the study period	87 (100%)	34 (100.0%)	-1.0, 5.0 (-13.0-10.0)	53 (100.0%)	0.0, 6.0 (-21.0-6.0)
Change in EQ5D index value over the study period**	87 (100%)	34 (100.0%)	-0.019, 0.251 (-0.487-0.521)	53 (100.0%)	0.071, 0.172 (-0.368-0.502)
Change in EQ5D health thermometer score over the study period	82 (94.3%)	29 (85.3%)	-5.0, 33.0 (-40.0-40.0)	53 (100.0%)	0.0, 18.0 (-50-30)

**Complete case data for all variables with the exception of EQ5D health thermometer (94.3%) with five individuals in the control arm missing baseline EQ5D health thermometer scores in whom we were unable to calculate a change over the study period.*

Included in both our Intervention and Control cohorts were participants who had already completed Pulmonary Rehabilitation prior to the study start and, in addition, those who were already under the care of the local Secondary Care Respiratory Physicians. We looked separately at these subgroups to see if there was the suggestion of any influence on the results (

Table 5-9 and

Table 5-10). These groups were so small no inferences could be drawn.

Table 5-9 Change in symptom scores at twelve month follow up in those participants already completed pulmonary rehabilitation at baseline.

Symptom score	N (% data collection)	Control arm (N=14)		Intervention arm (N=24)	
		N	Median, IQR, (range)	N	Median, IQR, (range)
Change in CAT score over the study period	35 (92.1%)	13 (92.9%)	-3.0, 11.5 (-19.0-4.0)	22 (91.6%)	-5.0, 6.8 (-12.0-6.0)
Change in GAD-7 score over the study period	35 (92.1%)	13 (92.9%)	1.0, 3.0 (-8.0-6.0)	22 (91.6%)	0.0, 6.0 (-9.0-16.0)
Change in PHQ-9 score over the study period	35 (92.1%)	13 (92.9%)	2.0, 6.0 (-13.0-10.0)	22 (91.6%)	-1.0, 7.0 (-12.0-5.0)
Change in EQ5D index value over the study period	35 (92.1%)	13 (92.9%)	0.015, 0.319 (-0.295-0.521)	22 (91.6%)	0.054, 0.223 (-0.255-0.335)
Change in EQ5D health thermometer score over the study period	32 (84.2%)*	10 (71.4%)	-2.5, 29.0 (-25.0-35.0)	22 (91.6%)	0.0, 17.0 (-50.0-30.0)

**Missing scores represent those individuals lost to follow up in each arm with the addition of three individuals in the control arm missing baseline EQ-5D health thermometer scores in whom we were unable to calculate a change over the study period.*

Table 5-10 Change in symptom scores at twelve month follow up in those participants with a confirmed COPD diagnosis, not under active Respiratory Physician care and had not completed Pulmonary Rehabilitation at baseline.

Symptom score	N (% data collection)	Control arm (N=24)		Intervention arm (N=36)	
		N	Median, IQR, (range)	N	Median, IQR, (range)
Change in CAT score over the study period	49 (81.7%)	19 (79.2%)	-4.0, 5.0 (-15.0-8.0)	30 (83.3%)	-4.0, 7.8 (-20.0-8.0)
Change in GAD-7 score over the study period	49 (81.7%)	19 (79.2%)	0.0, 8.0 (-13.0-2.0)	30 (83.3%)	0.0, 4.0 (-6.0-9.0)
Change in PHQ-9 score over the study period	49 (81.7%)	19 (79.2%)	-2.0, 4.0 (-13.0-10.0)	30 (83.3%)	-0.5, 5.0 (-21.0-6.0)
Change in EQ5D index value over the study period	49 (81.7%)	19 (79.2%)	0.000, 0.193 (-0.487-0.267)	30 (83.3%)	0.059, 0.204 (-0.368-0.502)
Change in EQ5D health thermometer score over the study period	47 (78.3%)*	17 (70.8%)	5.0, 35.0 (-35.0-40.0)	30 (83.3%)	-1.0, 20.0 (-25.0-20.0)

**Missing scores represent those individuals lost to follow up in each arm with the addition of two individuals in the control arm missing baseline EQ5D health thermometer scores in whom we were unable to calculate a change over the study period.*

Table 5-11 shows the hospitalisation rates between the study Intervention and Control groups over the study period. The table also shows the rates when adjusted for those with a confirmed diagnosis of COPD and for those not already under the care of a Respiratory Physician at study baseline. This suggests the number of participants hospitalised over the study period for a respiratory illness was less in the intervention than the control arm in those with a confirmed diagnosis of COPD (hospitalisation rate 3 participants vs 0 participants).

Table 5-11 Table demonstrating hospitalisation rates over the Study Period.

Cohort	N (% data collection)	Control arm		Intervention arm	
		N	Number hospitalised	N	Number hospitalised
All individuals followed to twelve months	104 (100.0%)	37	3.0 (8.1%)	67	2.0 (3.0%)
Those individuals with confirmed COPD diagnosis only	87 (100.0%)	34	3.0 (8.8%)	53	0.0 (0.0%)
Those with confirmed COPD diagnosis and NOT already under Respiratory care.	76 (100.0%)	29	2.0 (6.9%)	47	0.0 (0.0%)

Exacerbation rates for the same groups is shown in **Error! Not a valid bookmark self-reference.** . This does not suggest an obvious difference between the groups although there may be a slight suggestion of a small reduction in exacerbation rate in the intervention arm in those patients with confirmed COPD and not already under the care of a Respiratory Physician.

Table 5-12 Table demonstrating exacerbation rates over the Study Period.

Exacerbation Rate Cohort	N (% data collection)	Control arm (N=24)		Intervention arm (N=36)	
		N	Median, IQR, (range)	N	Median, IQR, (range)
All individuals followed to twelve months	104** (100.0%)	37	1.0, 3.0 (0.0-7.0)	67	0.0, 1.0 (0.0-4.0)
Those individuals with confirmed COPD diagnosis only	87 (100.0%)	34	1.0, 2.0 (0.0-7.0)	53	1.0, 1.0 (0.0-4.0)
Those with confirmed COPD diagnosis and NOT already under Respiratory care.	76 (100.0%)	29	1.0, 2.0 (0.0-7.0)	47	0.0, 1.0 (0.0-4.0)

***Three individuals moved GP practice so GP reported exacerbation data not available, in these cases, patient reported data used.*

The number of patients attending acute Pulmonary Rehabilitation during the study period was considerably higher in the Intervention arm. This difference reduced in those with a confirmed diagnosis of COPD (2 vs 11). The difference reduced further when those under Respiratory Physician care at study baseline were removed (2 vs 9) (Table 5-13).

Table 5-13 Table demonstrating Pulmonary Rehabilitation rates over the Study Period.

Cohort	N (% data collection)	Control arm		Intervention arm	
		N	Number completed or attending Pulmonary Rehabilitation	N	Number completed or attending Pulmonary Rehabilitation
All individuals followed to twelve months	104 (100.0%)	37	2 (5.4%)	67	14 (20.9%)
Those individuals with confirmed COPD diagnosis only	87 (100.0%)	34	2 (5.9%)	53	11 (20.8%)
Those with confirmed COPD diagnosis and NOT already under Respiratory care.	76 (100.0%)	29	2 (6.9%)	47	9 (19.1%)

After the final study review the study participants were given a feedback form to complete and return (At this point the Intervention arm participants had received the full study intervention of clinical review by the Clinical Fellow and the Control arm participants had received a review by the study Specialist Respiratory Nurse at their finial review appointment). 63 participants of the 104 followed to study completion returned their feedback form but not all participants responded to all questions hence the different question response rates (Table 5-14).

The participants in the Intervention arm reported a more positive effect on their lung health than the Control arm. They felt the impact on their general health was also positive. All the elements of the study design highlighted were considered important to most of the participants with no suggested difference between the Control and Intervention arms. No participant that responded via the feedback forms felt the study had negatively impacted on their lung or general health. In general, the comments received were very positive and many participants commented on the improvement seen in the confidence, motivation to exercise and quality of life.

Table 5-14 Patient Feedback. Table displaying the responses on the feedback forms returned after study completion.

Feedback Question	Response rate** (percentage)	Control population (N=18)	Intervention population (N=46)
What effect has taking part in the study had on your lung health?	62 (96.9%)		
Very positive		4 (22.2%)	12 (27.3%)
Positive		5 (27.8%)	24 (54.5%)
No effect		9 (50.0%)	8 (18.2%)
Negative		0 (0.0%)	0 (0.0%)
Very negative		0 (0.0%)	0 (0.0%)
What effect has taking part in the study had on your general health?	61 (95.3%)		
Very positive		4 (22.2%)	8 (18.6%)
Positive		6 (33.3%)	20 (46.5%)
No effect		8 (44.4%)	15 (34.9%)
Negative		0 (0.0%)	0 (0.0%)
Very negative		0 (0.0%)	0 (0.0%)
Were the following important to you?			
The study location being in your GP surgery	63 (98.4%)		
Important		16 (88.9%)	42 (93.3%)
Not important		2 (11.1%)	3 (6.7%)
Being able to see a lung expert	61 (95.3%)		
Important		18 (100%)	42 (97.7%)
Not important		0 (0.0%)	1 (5.3%)
Good communication between the visiting Doctor and your GP	56 (87.5%)		
Important		14 (82.4%)	37 (94.9%)
Not important		3 (17.6%)	2 (5.1%)
Being able to talk about all your concerns	61 (95.3%)		
Important		18 (100%)	42 (97.7%)
Not important		0 (0%)	1 (2.3%)

*** A total of 64 participants returned forms however not all forms were fully completed hence the differing number of responses to each question.*

5.3.2 Discussion

Whilst we were not able to demonstrate an improvement in the suggested Primary endpoint of CAT score in this feasibility study the study remains of value and demonstrated that a proactive review facilitated a management plan that encouraged improved diagnostic accuracy and concordance with Primary Care COPD management as suggested by the GOLD guidelines. In particular, encouraging increased participation in Pulmonary Rehabilitation given the evidence base regarding improvement in quality of life, exercise tolerance and mortality is a very positive finding, particularly as most participants completed the course [8]. This additional attendance, above that already achieved by the Practice nurses is likely to reflect the additional time spent

with the patient and the specialist knowledge around what exactly the classes comprise. Many COPD patients lack confidence and finding transport to the classes can seem overwhelming. Being able to understand exactly what the classes would entail, that transport could be provided and being reassured that the exercises would be altered to accommodate their individual needs seemed likely to increase the chance of a patient attending. That most of those patients then completed the course does also suggest that the expectation given was realistic and patients generally reported Pulmonary Rehabilitation as being a very positive experience. In the Clinical Commissioning Group in which the study was conducted, Pulmonary Rehabilitation is funded and available for those with chronic asthma, bronchiectasis and interstitial lung disease, hence the attendance of some patients without a confirmed COPD diagnosis. A further development of the study design could be a qualitative piece of work exploring with the participants what influenced their decision to attend Pulmonary Rehabilitation and a similar piece with the Practice nurses exploring the barriers perceived in their referrals.

There was the suggestion of an improvement in the EQ5D index score, a measure of functional quality of life and over 80% of the 68.7% of the Intervention arm participants who returned the feedback forms also considered that the study had impacted either positively or very positively on their lung health with 65.1% feeling the study had impacted positively or very positively on their general health.

In addition to these subjective outcomes there was a suggestion that the Intervention arm clinical review may influence the rates of exacerbation and hospitalisation. Whilst the numbers in this study are small, the improvement in exacerbation rate and hospitalisation is a clinically relevant finding given the well evidenced association between exacerbation rates, hospitalisation, deterioration in lung function and mortality [16-18]. This reduction in hospitalisation rates would certainly be worth further study as it was also seen in the work done by Gillett, Lippiett & Astles [187]. However it is important to note that as many of their participants were asthmatics started on ICS their study findings are not likely to represent quite the same change.

In general, the end points used for this study all warrant further investigation although considering the findings seen in this study, a change in CAT score may not reflect the best choice of primary endpoint. As we have learned through the process of the study it has become clear that the symptom scores (CAT, GAD-7 & PHQ-9) and the quality of life scores are certainly useful information and very relevant but are impacted upon by so many different factors (many outside the control of a research study), that they may confound study results when used as primary endpoints and may be better used in a secondary capacity. The finding of possible improvement

in hospitalisation and exacerbation rates was unexpected but very positive and is specific to COPD so may represent a better primary endpoint. Similarly useful as a primary endpoint would be referral and completion rates to well evidenced treatments such as Pulmonary Rehabilitation and, diagnostic confirmation or change rates.

The study would have benefitted from a much more in depth and developed qualitative aspect to further explore the impact on the participants (patients and staff) perhaps both immediately after the intervention and after the twelve month interval to explore the longevity of any changes seen and on one further occasion to explore the staff opinions around the study findings.

Consideration would need to be given to the inclusion criteria around those already managed in outpatient secondary care and what follow up was offered to those who are not found to meet the criteria of a COPD diagnosis at initial intervention. Following those patients who have had a diagnosis changed with qualitative aspects of the study and quality of life measures may be appropriate but following them with COPD specific measures is clearly not appropriate and this may confound the study results.

5.4 General Discussion

5.4.1 Study design and analysis

A cluster randomised trial is one in which the unit of randomisation is something other than an individual. Cluster randomised trials are commonly used to investigate a change in workplace based practice, new protocol or guideline, where, if patients are randomised individually the risk of contamination in the trial is high. As the practitioners delivering the Intervention are also delivering the control standard of care they are likely to unconsciously bring aspects of the intervention into the care of the Control arm patients. Reducing contamination is one of the strengths of a cluster-based study design. The intention of this study was to feed back the results of an assessment of an individual and suggestions for optimisation of their COPD and other comorbidities to their GP and Practice Nurse which they would enact, thereby increasing education and awareness in the Primary Care Practice MDT. Clearly, the risk of contamination was high if Control and Intervention arm participants were recruited from the same Primary Care Practice so clustering the recruitment of participants by Practice to either Control or Intervention arm was appropriate.

A significant limitation of cluster randomised trials is the confounding effects of the individual environments that represent the clusters. In the case of our study the difference in Practice size, level of engagement and their patient demographics had a significant effect on our results as discussed further in section **Error! Reference source not found.**. The confounding nature of the cluster design was acknowledged at the study start and attempt was made to minimise this by matching the Practices by size prior to randomisation. Initially it was considered that as all the Primary Care Practices were drawn from a small geographical location in an inner city residential area with significant poverty and deprivation levels they would be well matched. Upon reflection, enough consideration has not been given to the impact of the study on different Primary Care Teams and individual circumstances. Some changes of staffing took place in the individual Practices which could not have been anticipated at the study start by someone not working within the Practice, and also noticeable was the effect on the entire study population of the increasing pressures on Primary Care during the study period. As previously mentioned, these participants were a relatively deprived and comorbid set of individuals and their difficulties obtaining appointments and struggling with management of their chronic diseases at a time of increasing pressure on Primary Care were apparent throughout the reviews. This was particularly noticeable in the largest GP Practice in the Intervention arm (32 participants) where, within the first six months of the study, the GP Partners resigned in a stepwise fashion due to overwhelming working pressures. At 12 months the practice was struggling with insufficient staffing and was placed in special measures by the Care Quality Commission during the period the final reviews took place. Many participants in this Practice commented on their distress at the situation, their difficulty gaining a GP appointment and the negative impact they felt this was having on their health. A similar set of circumstances was occurring in one of the Control Practices, however the GP Partners had not yet resigned so there was significantly less impact on the study Control participants. In a future study we would be more aware of the difference in impact on a Practice dependent on the pre-existing Practice circumstances and previous experiences of the staff working within the Practices and how this may act on the consequent change seen. This confounding factor will always be present to some degree in any trial and amplified in a cluster based study design but would be minimised in a study with more clusters.

One of flaws in the study design was a lack of appreciation of the effect of a cluster-based analysis on the sample size calculation. The sample size calculation was based on the number of individuals required to show a minimum clinically important difference in CAT score of 2.9 in an individual randomised controlled trial. In a cluster-based analysis this number should rather be a starting guide to the number of individuals within a cluster with further calculation required to

take into account both the intracluster correlation coefficient (how closely the outcome measures from the individuals within a cluster are correlated) and the number of clusters available or required [204]. In our study, the number of clusters was fixed due to the inefficiency of our finite resource of study staff travelling between Primary Care Practices. Had this been appreciated earlier in the study it would have been clear that we did not have sufficient staffing to undertake an effectiveness study of the magnitude required. This and under recruitment, disproportionately so, to the control arm led to the study being significantly (and disproportionately to the Control arm) underpowered.

In hindsight, under recruitment to the Control arm also reflected a flaw in study design which had also inadvertently allowed selection bias. As the Primary Care Practices had already been randomised at the point of participant recruitment, the Intervention arm offered individuals the opportunity to be assessed by a Speciality Respiratory Physician, not offered to those in the Control Arm. These individuals were rather offered a review by a Specialist Research Nurse at the end of the Study (at the time of recruitment over a year away) which is likely to have negatively affected recruitment to the Control arm. Patients may not have understood the difference between their Practice “COPD” Nurse reviews and a Speciality Nurse review, in addition, a Physician review may have been viewed as bigger enticement. As part of the recruitment process, the CAT score was also performed over the telephone by different individuals for each study arm with the Speciality Respiratory Physician recruiting and consenting patients for the Intervention Arm and the Specialist Nurses recruiting and consenting for the Control arm. Whilst every endeavour was made to keep the approach consistent there is likely to have been differences in both the researcher’s approach to the participants resulting in some selection bias.

The consequence of the error in sample size calculation and under recruitment led to the study being underpowered for an individually randomised trial and even more so for a cluster based study. The analysis approach initially used was that of an effectiveness **individually** randomised controlled trial. In the setting of the effectiveness **cluster** randomised controlled trial this was intended to be, account should have been taken of the impact of the clusters themselves on the study results in the statistical analysis. In addition, the study was so significantly underpowered in this situation that any statistical significance assigned to the results was likely to be subject to significant type 2 error. The study numbers were simply too small for any assessment of statistical significance to be drawn.

5.4.2 Future research

Taking into consideration the lessons learnt from this study a future study should have a more consistent recruitment process across the cohorts, ideally recruiting participants before the cohorts are randomised and ensuring the recruitment process is delivered by the same individuals across the cohorts thus avoiding selection bias. To minimise disproportionate under recruitment and attrition in the Control arm it may be more appropriate to offer speciality review by the same health professionals to all. An option may be to consider using a cross over study design to maximise recruitment.

Overall, as a feasibility study, we have demonstrated that it is reasonable to go on to investigate proactive Specialist review in Primary Care as an intervention but that the intervention would need to take a slightly different form. Suggesting that every individual with COPD should be reviewed by a Secondary Care Respiratory Physician is financially and logistically impractical as they are an expensive finite resource. To develop these research findings further into a larger scale trial aiming for a widely adopted management approach, the intervention should be something financially and logistically feasible with practical clinical utility. A pilot study with a similar patient facing intervention delivered by Speciality and Generalist Nurses (as seen as part of the Gillet, Lippiett, Astles et al paper) would be a possibility to see if similar positive effects such as those seen in this study and in their study in 'high risk' patients could be replicated. A more efficient and realistic use of Speciality Physician time may be in the 'lighter touch' form of an integrated MDT, a learning environment to which members of the Primary Care MDT are able to seek advice without formal patient referral.

A discussed previously, the classification of the endpoints of the study should be reviewed to try to minimise the study being confounded by outside factors, considering diagnostic clarity,referral to aspects of standard care such as Pulmonary Rehabilitation, hospitalisation and exacerbation rates as primary endpoints. However, there is likely to be value in all the endpoints suggested previously, particularly in the form of a bigger randomised controlled trial where a necessary part of the analysis will be a health economic evaluation where quality of life scores can significantly contribute. A qualitative element to a future study is essential to explore the impact on, and motivations of participating staff and patients and further explore the importance of aspects such as the study location and design.

5.5 Conclusions

This study was initially designed as a cluster randomised controlled effectiveness study. As the study progressed it became clear the study design and, in particular, the sample size calculation and analysis were flawed.

Whilst the study was underpowered and had consequent limitations as a randomised controlled trial, when rewritten as a feasibility trial it has significant utility. The findings suggest that in a further refined form, a proactive speciality clinical review in Primary Care may cause improved health outcomes and potential financial savings in patients with COPD deemed low risk by DOSE score and warrants further study.

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6 Overall Thesis Discussion

6.1 Discussion

6.1.1 Key findings from the thesis

We aimed, firstly, to establish in a clinical study if a proactive specialist respiratory review could improve health outcomes in a Primary Care COPD Population deemed low risk by DOSE score, and, secondarily, to develop a database approach that could be pre-emptively used to risk stratify this group of individuals into those at the highest risk of future deterioration.

In the database study, we developed a Read code set and algorithm which allows the application of the DOSE score to real world Primary Care patient records and the identification of a number of relevant comorbidities and demographics. Using the negative health outcomes of a deterioration into a high risk DOSE score, a change in DOSE score of two points (DOSE scores are not strictly a health outcome themselves but have well evidenced associations with poor health outcomes), hospitalisation and death during the study period, we assigned patients, low risk by DOSE score, into more rapidly or slowly deteriorating cohorts. We went on to use bivariate analysis and then forward conditional modelling to produce a risk stratification model that allocated patients to the rapidly deteriorating cohort based on their comorbidities and demographics. This model had a predictive probability, comparable to other validated risk prediction scores. We have also suggested how this might be further developed into a model with increased clinical utility by including an intrinsic management plan in the model design.

The clinical study was originally developed as a cohort randomised controlled efficiency study but in this form was recognised to have significant flaws in study design, sample size and analysis. Rewritten as a feasibility study it was not able to demonstrate an improvement in symptom based scores (CAT score, PHQ-9, GAD-7 or EQ5D/ health thermometer) but remained a valuable piece of work.

As a feasibility study we were able to demonstrate it was possible to recruit patients to a clinical study of this design but the recruitment strategy needs further development to ensure adequate recruitment in the control arm and to avoid selection bias. Retention to the study was reasonable but the attrition slightly higher than the 10% we had initially anticipated which would need to be taken into account in any further development of the research. The clinical study demonstrated there were no obvious clinical or logistical barriers to a speciality review in low risk COPD patients

Primary Care but the intervention would need further development for use in future research, Specifically, a Speciality Registrar is a finite resource which would limit the ability of this intervention to be reproduced at any sort of scale and is an expensive member of medical staff so is unlikely to be cost efficient used in this way. Whilst we were not able to demonstrate an improvement in our defined endpoints in this feasibility study, we did demonstrate positive findings in terms of change of diagnosis, alterations in inhaled medications and increased referral rates to management strategies such as Pulmonary Rehabilitation, well evidenced to improve health outcomes. The study also suggested there may be an improvement in hospitalisation rates in patients with COPD in the Intervention arm. Whilst this was a small feasibility study so could not demonstrate any difference with statistical significance, this adds to the study findings that further development of this research is likely to add to the current body of literature.

6.1.2 Reflections on the thesis findings and its place in the current body of literature

A key strength of the database study was the demonstration that it is possible to administer the DOSE score in real world Primary Care records giving the approach clear clinical utility. The majority of the historical evidence base for COPD treatment is generated using research patient cohorts with a robust diagnosis. Throughout both studies, the theme of incomplete or conflicting data recording has impacted on the study results. Clearly there are many reasons why this is the case in real world databases and in the main, it does not necessarily reflect poor clinical care but missing or inaccurate data is problematic for both the patient and the Primary or Secondary Care Practice utilising the patient records. It could be argued that, as the database study was only able to create a DOSE score for just over half the patients in the COPD database population, developing a software approach for use in patient facing care does not have clinical utility (The Clinical study supported the Database study findings, with the diagnosis of COPD found to be inaccurate in 20% of the Intervention arm participants). We would argue that if Primary Care Practices were to use the DOSE score to risk stratify their patients, obtaining the information regarding missing score components is itself of clinical utility. Without the components of the DOSE recorded appropriately (all QOF targets), Primary Care Practices may not meet their QOF targets and miss out on payments. Identifying which patients do not have the components of a DOSE score recorded will not only identify the proportion of patients in whom the data is recorded in manner not reflective of the care they have received but also, the proportion truly missing out on clinical care. This could improve clinical efficiency in Practices and identify vulnerable patient subgroups. This has particular clinical utility when those patient with missing data appear to have poorer health outcomes and higher mortality [59] (Section 3.1).

Another strength of the study was the development of the DOSE score algorithm and the DOSE score components, demographic and comorbidity code sets themselves which add to the literature base on the subject. Other methods for coding COPD, exacerbations and various comorbidities already exist in the literature and that the strategies used differ between different research groups is a limitation of all research in the area. A consideration when moving forward would be whether to add our current coding methods to the databases being developed for this purposed to align coding methods between research groups and thereby enable the direct comparison of results, or to simply consider adopting the coding methods used by one of the larger research groups to make our future studies directly comparable with the largest bodies of work in the literature.

On a similar theme, the development of the risk stratification model is a strength of the work as it adds to the current body of research stratifying risk by comorbidity in COPD patients in Primary Care. However, in using more than one outcome to allocate patients to the rapidly deteriorating group it is difficult to robustly compare the model to other risk stratification scores. Similarly, using an outcome such as a change in DOSE score which it likely to represent a poorer state of health but does not have a body of evidence to demonstrate this, adds to the difficulties in evaluating the risk stratification model. In learning through the process of this research we appreciate that using strategies and outcomes that already have a research/validation body behind them would have simplified the research process and made it easier to analyse and compare the utility of the results with existing work.

Another area when we have demonstrated learning through the process of the thesis development is in the significant changes to the methodology made to the clinical study from a cohort randomised, controlled efficacy study to a feasibility study. Upon reflection, the flaws in the study methodology arose due to a lack of experience and understanding of study design on the part of the researcher. Through the process of undertaking the study and analysing and discussing the results the researcher has developed a greater understanding of the use of feasibility and pilot studies in the development of randomised control trials to assess the pitfalls of well intentioned study designs when they are put into practice. The researcher has also developed a greater appreciation and understanding of the value of simplicity within a research trial of any description, when trying to minimise confounding factors and make the results comparable to other studies. In hindsight, an intervention that followed the same principles and structure but was carried out by a member staff who would more realistically be available to see patients in a scaled up trial or in a real world NHS settling would have added to the clinical utility

of the trail and its potential to be part of a model of care that could be adopted into widespread use.

A key strength of the clinical study were the changes in diagnosis and treatment effected in the interventions arm. A change in diagnosis in 35.5% of patients adds to the previously discussed body of literature suggesting many patients with COPD are misdiagnosed. As do the 77.6% of patients with changes to their inhaled therapies and the referral to over a quarter of people to pulmonary rehabilitation. The inhaled therapy changes are large number and higher than that seen in the trials discussed in the literature review however these are a different subset of patients and the subsequent effects on wellbeing and health economics of adding bronchodilator therapies in COPD are not likely to be comparable to adding inhaled steroids in asthma. The size and design of the study limit the conclusions that can be drawn from these findings but this provides a strong basis for investigating whether this could be reproduced by other members of the MDT at a larger scale and the effect this might have on subsequent health outcomes.

As discussed previously, the study was rewritten as a feasibility study rather than being designed as such and one of its key limitations was the lack of a qualitative element which could have far better explored the effect of the intervention on the individual participants and the Primary Care Practices involved. An important part of any research going forward would be measuring the longevity of the effect of any intervention made with regards to change in practice of the members of the Primary Care Practice staff and this would be likely to be best measured with a combination qualitative and quantitative approach.

6.1.3 Implications of the work in future research and practice

These studies add to the body of research on Primary Care COPD risk stratification and management. The database study provides further evidence for the impact of comorbid illness on prognosis in COPD and alternative strategies for coding COPD, various comorbidities and patient demographics all of which could be adopted for use in future research. The demonstration that the DOSE score is easily utilised in real world clinical records adds a further evidence base to the already extensive validation of this risk stratification score.

The risk prediction model represents a useful starting point but would need further development and validation to give it helpful and realistic clinical utility in Primary Care. Future studies should be directed at further development of the model with the outcomes separated (for example, separate outcomes of death and hospitalisation) to allow direct comparison to other existing models and specifically to ensure that the model has a predictive probability above that when

compared to DOSE alone, with regards to hospitalisation and death. It would also be reasonable to extend the research to look further into the relationship between a deterioration in DOSE score and poor prognostic outcomes where the DOSE score still remains <4. This could represent another strategy for identifying patients early on a rapidly deteriorating path.

Ultimately the aim would to be to develop a risk prediction model further into a scoring system with cut points to stratify patients into levels of risk. For the score to have clinical utility outside a research environment we would need to demonstrate that the risk factors were modifiable, perhaps by focusing a clinical review on those co-morbidities which are shown to confer the risk in the model and to understand whether optimising those co-morbid illnesses could improve patients' subsequent clinical path.

The clinical study adds to body of research indicating there is likely to be value in specialist review of COPD in Primary Care. Given the results of the feasibility study, the next steps in the development of this concept and method of delivering care would be to redesign a pilot study to develop an intervention that could use the same clinical review structure but could be delivered by a different member of the MDT in a way more likely to be cost efficient and feasible to be delivered at scale. There would need to be a more formal, qualitative portion of the study, exploring the impact on the Primary Care service itself and on the individuals involved. It would be feasible to use the same outcomes but with modified ranking and, in addition, to consider the inclusion of outcomes such as diagnosis change, medication change and referral to pulmonary rehabilitation.

Our database study outcomes support the association between depression and a rapidly deteriorating subgroup in COPD patients [88, 89]. There is evidence to suggest that only a third of patients with co-existent depression will be treated [98] and whilst there is no strong evidence to suggest that treating depression improves outcomes in COPD, one can easily extrapolate that the effect of depression-related poor memory, motivation and reduced exercise levels may well prove to barriers to the mainstays of proven COPD management strategies such as Pulmonary Rehabilitation and self-recognition and management of acute exacerbations. Considering this, it is a very reasonable research question to establish if optimisation of mental health needs might improve COPD outcomes and /or smoking cessation rates. Our feasibility study did not suggest an improvement in the Intervention arm, where, there was no suggestion of improvement of depression and anxiety scores despite addressing these issues with the participants and referring on to the Community Mental Health services available. It may be, that this was because the premise for the study was to utilise the resources already present in Primary Care, and, in the

case of Mental Health treatment, these resources are considerably under-resourced, and the waiting time is significant. The nature of the symptoms of anxiety and depression suggests that individuals are likely to struggle to be confident and motivated enough to be able to access treatment for themselves and upon reflection, the single six week follow up appointment offered during the study was not optimal to provide the follow up support needed for this aspect of these participants' care. In future studies, the model of clinical review would need to be altered if the study aims to make a significant impact on the study populations' Mental Health and this is such a complex, multi-faceted issue. It would probably be better addressed in as a separate research question and would need a study specifically designed to answer this question with resource included to offer the treatment, available in the NHS as standard care but that is realistically delivered in a real-world timeframe far beyond that of a study intervention period.

In summary, the optimal end goal would be to combine the concepts behind the database study and the clinical study in a large scale trial investigating early proactive speciality review in individuals with low risk COPD identified by a risk stratification model as vulnerable to deterioration in the near future. The comorbidities identified as conferring a poorer prognosis in the risk stratification model would provide an intrinsic management plan to structure the holisitic medical review.

6.1.4 Conclusions

Why is it important to develop this research and proactively seek out individuals for management in a health service where finances and clinical personnel are under such tight constraints?

The patient feedback comments from the Clinical study reflects participants' clinical improvement and empowerment through education and increased confidence.

"Owing to my breathing being that little better, I had more confidence when out walking which I still do and enjoy. Just talking to an expert in COPD makes all the difference"

"I have a better understanding of COPD. It made me look at the positive side of my health and not so much the COPD which can sometimes make things more negative than they need to be."

"I felt more confident and less anxious when taking part in the study"

"Pushed me into thinking more about my condition. Caused me to actually exercise more."

"I now understand more about the effects and ways of coping with it [COPD]. It has encouraged me to exercise and walk more and to try a different inhaler which has been so much better for me. I liked the one to one talks and questions answered."

"Am walking more. Walking is hard but you have to DO it."

In the introduction of this thesis we discussed the significant financial cost and loss of quality of life seen in COPD, worldwide and in the UK and these costs continue to rise [2, 3, 7, 8]. We have demonstrated there are well evidenced treatments for COPD with proven cost benefit that are not being accessed. Some of the reason for this may be that due to the nihilism of medical professionals and the shame that exists around a COPD diagnosis [182]. Patients may not present to medical services until their disease burden is already significant and COPD associated physical and mental health comorbidities are already well established. At this point it is often considerably more difficult or too late to alter behaviours and beliefs established around the disease. If patients were pro-actively educated earlier in their disease process when they are less likely to be so significantly anxious around their symptoms and have yet to develop established health beliefs they may be more likely to be able to engage in education program and so be able to take advantage of the treatment options available to them.

If our current reactive management approach continues as it has done, the financial and morbidity burden of COPD it likely to continue to rise. One could argue that we cannot afford not to take a different, more proactive approach to the management of COPD.

6.2 Overall Thesis Conclusions

We aimed, firstly to establish if a proactive specialist clinical review could improve health outcomes in a Primary Care COPD population deemed low risk by DOSE score, and, to develop a database approach that could be pre-emptively used to risk stratify this group of individuals into those at the highest risk of future deterioration.

We developed a database approach which can be used to apply the DOSE score to a Primary Care COPD population using real world Primary Care records and can identify various comorbidities and patient characteristics. We have presented a risk stratification model which can identify a subgroup of patients deemed low risk by DOSE score who are at higher risk of rapid clinical deterioration, using their documented clinical characteristics and comorbidities. We have suggested an example of how this may be developed further into a model which forms the basis of a pro-active management plan to address known risk factors in COPD.

We were not able to demonstrate that a proactive specialist clinical review of COPD patients, low-risk by DOSE score, improved COPD symptom burden at twelve months by quality of life measures. In its original conception as a cohort randomised controlled efficiency study our trial design was significantly flawed but as a feasibility study it suggested there is feasibility and value in further investigating the effect of pro-active specialist clinical review of these low risk Primary Care COPD patients but with modified endpoints and the intervention in a modified, more cost efficient form which could then be reproducible in a real life NHS environment, at scale.

COPD is a leading cause of hospital admission and healthcare utilisation in the United Kingdom. Further investigation is warranted as to whether this research could be further developed with a view to decreasing the financial and symptomatic burden of COPD in the United Kingdom.

Appendices

Appendix 1. The COPD Assessment Test [205]

Your name:

Today's date:

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	

Last Updated: February 24, 2012

Appendix 2. The Read codes and terms used to define diagnosis of COPD.

H3...	Chronic obstructive pulm.dis.
H31..	Chronic bronchitis
H310.	Simple chronic bronchitis
H3100	Chronic catarrhal bronchitis
H310z	Simple chronic bronchitis NOS
H311.	Mucopurulent chr.bronchitis
H3110	Purulent chronic bronchitis
H3111	Fetid chronic bronchitis
H311z	Mucopurulent chr.bronchit.NOS
H312.	Obstructive chronic bronchitis
H3120	Chronic asthmatic bronchitis
H3121	Emphysematous bronchitis
H3122	Acute exacerbation of COAD
H3123	Bronchiolitis obliterans
H312z	Obstructive chr.bronchitis NOS
H313.	Mixd simp+mucopur chron bronch
H31y.	Other chronic bronchitis
H31y1	Chronic tracheobronchitis
H31yz	Other chronic bronchitis NOS
H31z.	Chronic bronchitis NOS
H32..	Emphysema
H320.	Chronic bullous emphysema
H3200	Segmental bullous emphysema
H3201	Zonal bullous emphysema
H3202	Giant bullous emphysema
H3203	Bullous emphysema + collapse
H320z	Chronic bullous emphysema NOS
H321.	Panlobular emphysema
H322.	Centrilobular emphysema
H32y.	Other emphysema
H32y0	Acute vesicular emphysema

H32y1 Atrophic (senile) emphysema

H32y2 MacLeod's unilateral emphysema

H32yz Other emphysema NOS

H32z. Emphysema NOS

H36.. Mild chron obstr pulm disease

H37.. Mod chron obstr pulm disease

H38.. Sev chron obstr pulm disease

H39.. Very severe COPD

H3A.. End stag chron obst airway dis

H3y.. Chronic obstr.airway dis.OS

H3y0. Chr obs pulm dis+ac l resp inf

H3y1. Chr obs pulm dis+ac exac,unspc

H3z.. Chronic obstr.airway dis.NOS

H4640 Chronic chemical emphysema

H4641 Chemical obliter.bronchiolitis

Hyu30 [X]Other emphysema

Hyu31 [X]O spcf chron obs pulmon dis

Appendix 3. The Read codes and terms used to define mMRC score, FEV1 and smoking status.

mMRC Score

Each MRC breathlessness score assessment date and result value were recorded during the study period. The number of assessments per patient varied from a minimum of one (or none) to a maximum of 24 assessments. Any duplicated records were excluded from the dataset.

Read codes used: 173H., 173I., 173J., 173K., 173L. with corresponding terms 'MRC_Asmt_Date_1' and 'MRC_1'.

Of note, the Read code entries denote MRC score rather than modified MRC score used in the DOSE calculation, therefore this was modified accordingly in the DOSE score calculation.

FEV_1 Percentage of Predicted

Each FEV_1 assessment date and result value was recorded during the study. The number of FEV_1 assessments per patient varied from a minimum of one (or none) to a maximum of 60 assessments. Any result values considered to be outside of the expected range were excluded (expected range was defined as values ≥0.2 litres and ≤ 7 litres or predicted values of ≥10% and ≤ 140%). Any duplicated records, and all assessments with a null or zero result value were excluded from the dataset.

Read codes used: 339b., 339O., 339e., 339a., 339f., 339S., 339S0. with corresponding terms 'FEV1_Asmt_Date_1'and 'FEV1_Value_1'.

Smoking Status

Each smoking status assessment date and result value (grouped into three smoking status options) were recorded during the study period. The number of smoking status assessments per patient varies from a minimum of one (or none) to a maximum of 219 assessments. Any duplicated records were excluded from the dataset.
Read codes used:
Smoker; 137., 1372., 1373., 1374., 1375., 1376., 137b., 137c., 137C., 137D., 137d., 137e., 137E., 137f., 137G., 137h., 137H., 137J., 137m., 137M., 137n., 137P., 137Q., 137R., 137V., 13p0.,13p5., 67H6., 745H., 8CAg., 8CAL., 8CdB., 8H7i., 8HBM., 8HBP., 8HkQ., 8HTK., 8IAj., 8IEK., 8IEM., 8IEo.,

8T08., 9hG.., 9hG0., 9hG1., 9kc.., 9kc0., 9kf1., 9kf2., 9ko.., 9N2k., 9N4M., 9Ndg., 9NdZ. , 9OO.., 9OO1., 9OO2., 9OO3., 9OO4., 9OO5., 9OO6., 9OO7., 9OO8., 9OO9., 9OOA., 9OOB., 9OOZ., 13p50%, 745H0%, 745H1%, 745H2%, 745H3%, 745H4%, 745Hy%, 745Hz%, 9NS02%, 9OOB0%, 9OOB1%, 9OOB2%.

Ex smoker; 137K., 137N., 137O., 137S., 137T., 13p4., 1377., 137l.,9km.., 137j., 1378., 137F., 137B., 1379., 137A., 137L., 137K0%.

Never Smoker; 1371. With corresponding terms ‘Smok_Stat_Asmt_Date_1, and ‘Smoking_Stat_1’

Appendix 4. The Read codes, Terms and algorithm used to define exacerbations

The date of each COPD exacerbation event recorded in primary care or secondary inpatient/A&E care was recorded during the study period. Only one event could be recorded every 21 days. The number of recorded COPD exacerbation events per patient varied from a minimum of one (or none) to a maximum of 160 events.

In isolation, either of the two Read codes below denoted a COPD exacerbation:

H3122 Acute exacerbation of COAD

H3y1. Chr obs pulm dis+ac exac,unspc

Alternatively, an exacerbation was defined by either any of the 48 Read codes used to define the COPD cohort in Appendix 2. The Read codes and terms used to define diagnosis of COPD., or, any of the 199 surrogate Read codes below denoting a COPD exacerbation with either code appearing up to seven days before or after a prescription for respiratory antibiotics and/or a prescription of corticosteroid

16L.. Influenza-like symptoms
171.. Cough
1713. Productive cough -clear sputum
1714. Productive cough -green sputum
1715. Productive cough-yellow sputum
1716. Productive cough NOS
1717. Night cough present
1719. Chesty cough
171A. Chronic cough
171B. Persistent cough
171C. Morning cough
171D. Evening cough
171F. Cough with fever
171H. Difficulty coughing up sputum
171L. Cough on exercise

171Z. Cough symptom NOS
172.. Blood in sputum - haemoptysis
173.. Breathlessness
1732. Breathless - moderate exertion
1733. Breathless - mild exertion
1734. Breathless - at rest
1735. Breathless - lying flat
1737. Wheezing
1738. Difficulty breathing
1739. Shortness of breath
173B. Nocturnal cough / wheeze
173b. Unab compl sentence one breath
173C. Short of breath on exertion
173D. Nocturnal dyspnoea
173F. SOB dressing/undressing
173g. Breathlessness csg diff eating
173G. Breathless - strenuous exertn
173Z. Breathlessness NOS
189.. Worsening exercise tolerance
1W0.. Possible influenza A vir H1N1
2322. O/E - dyspnoea
2324. O/E - respiratory distress
2DE3. O/E - respiratory obstruction
41D4. Sputum sample obtained
4E... Sputum examination
4E1.. Sputum examination - general
4E11. Sputum sent for examination
4E13. Sputum examination: abnormal
4E14. Sputum - not infected
4E1Z. Sputum gen. exam. NOS
4E2.. Sputum inspection

4E21. Sputum appears normal
4E22. Sputum: excessive - mucoid
4E23. Sputum: mucopurulent

4E24. Sputum: contains blood
4E25. Sputum: frothy/watery
4E26. Sputum: fetid/offensive
4E27. Clear sputum
4E28. Yellow sputum
4E280 Dark green sputum
4E281 Pale green sputum
4E29. Green sputum
4E290 Dark green sputum
4E291 Pale green sputum
4E2A. Sputum appearance
4E2C. Brown sputum
4E2D. White sputum
4E2E. Volume of sputum
4E2E0 Copious sputum
4E2E1 Moderate sputum
4E2E3 Scanty sputum
4E2F. Grey sputum
4E2G. Bloodstained sputum
4E2Z. Sputum inspection NOS

4E3.. Sputum microscopy
4E36. Sputum: pus cells present
4E37. Sputum: organism on gram stain
4E3Z. Sputum microscopy NOS
4E4.. Sputum culture
4EZ.. Sputum examination NOS
4I1E. Respiratory MC&S
4I2F. Lower respiratory sample
4JF5. Sputum sent for C/S
6635. Increasing exercise wheeze
663F. Oral steroids started
663L. Bronchodilators used > 1 /day
66Yg. COPD disturbs sleep
8BP8. AB therapy acute pulmon exacer

8H2R. Admit COPD emergency

8H7j. Refer respir rapid respon team

H0... Acute respiratory infections

H05.. Other acute upper resp.infect.

H051. Acute up resp tract infection

H05z. Upper respiratory infect.NOS

H06.. Acute bronchitis/bronchiolitis

H060. Acute bronchitis

H0600 Acute fibrinous bronchitis

H0601 Acute membranous bronchitis

H0602 Acute pseudomembranous bronch.

H0603 Acute purulent bronchitis

H0604 Acute croupous bronchitis

H0605 Acute tracheobronchitis

H0606 Acute pneumococcal bronchitis

H0607 Acute streptococcal bronchitis

H0608 Acute H.influenzae bronchitis

H060A Ac bronch/mycoplasma pneumonia

H060B Acut bronch due coxsackievirus

H060C Acut bronch/parainfluenza vir

H060D Acut bronch/resp syncytial vir

H060E Acute bronchitis/rhinovirus

H060F Acute bronchitis/echovirus

H060v Subacute bronchitis unspecif.

H060w Acute viral bronchitis unspec.

H060x Acute bact.bronchitis unspec.

H060z Acute bronchitis NOS

H062. Acute low respitract infection

H06z. Acute bronchitis/bronchiol.NOS

H06z0 Chest infection NOS

H06z1 Lower resp tract infection

H06z2 Recurrent chest infection

H07.. Chest cold

H0y.. Acute respiratory infectns.OS

H0z.. Acute respiratory infectn.NOS

H27.. Influenza

H271. Influenza + other resp.manif.

H2710 Influenza + laryngitis

H2711 Influenza + pharyngitis

H271z Influenza + resp.manifest.NOS

H27y. Influenza + other manifestat.

H27y0 Influenza + encephalopathy

H27y1 Influenza + GIT involvement

H27yz Influenza + other manifest.NOS

H27z. Influenza NOS

H30.. Bronchitis unspecified

H300. Tracheobronchitis NOS

H301. Laryngotracheobronchitis

H302. Wheezy bronchitis

H30z. Bronchitis NOS

H31.. Chronic bronchitis

H310. Simple chronic bronchitis

H3100 Chronic catarrhal bronchitis

H3101 Smokers' cough

H310z Simple chronic bronchitis NOS

H311. Mucopurulent chr.bronchitis

H3110 Purulent chronic bronchitis

H3111 Fetid chronic bronchitis

H311z Mucopurulent chr.bronchit.NOS

H312. Obstructive chronic bronchitis

H3120 Chronic asthmatic bronchitis

H3121 Emphysematous bronchitis

H312z Obstructive chr.bronchitis NOS

H313. Mixd simp+mucopur chron bronch

H31y. Other chronic bronchitis

H31y1 Chronic tracheobronchitis

H31yz Other chronic bronchitis NOS

H31z. Chronic bronchitis NOS

H3y0. Chr obs pulm dis+ac l resp inf

H460. Chemical bronchitis/pneumonit.

H4600 Acute chemical bronchitis

H460z Chemical bronch/pneumonit NOS

H59.. Respiratory failure

H590. Acute respiratory failure

H591. Chronic respiratory failure

H592. Chronic type 1 respir failure

H593. Chronic type 2 respir failure

Hyu0. [X]Ac upp respiratory infectns

Hyu04 [X]Flu+o rsp manif,flu v idntf

Hyu05 [X]Flu+o manifst,flu vir idntf

Hyu06 [X]Flu+o rsp manif,vir n idntf

Hyu07 [X]Flu+o maniftns,vir nt idntf

Hyu1. [X]Oth acute lowr resp infects

Hyu10 [X]Ac bronchitis/o spcf orgnsm

Hyu11 [X]Ac bronchltis/o spcf orgnsm

Hyu3. [X]Chron lowr respiratory dis

R06.. [D]Respiratory/chest symptoms

R0600 [D]Respiratory symptom unspec.

R0601 [D]Hyperventilation

R0602 [D]Orthopnoea

R0603 [D]Tachypnoea

R0606 [D]Respiratory distress

R0607 [D]Respiratory insufficiency

R0608 [D]Shortness of breath

R0609 [D]Wheezing

R060A [D]Dyspnoea

R060D [D]Breathlessness

R060z [D]Respiratory abnormalit.NOS

R062. [D]Cough

R063. [D]Haemoptysis

R0630 [D]Cough with haemorrhage

R063z [D]Haemoptysis NOS

R064. [D]Abnormal sputum

R0640 [D]Sputum abnormal - amount

R0641 [D]Sputum abnormal - colour

R0642 [D]Sputum abnormal - odour

R0643 [D]Abnormal sputum - tenacious

R064z [D]Abnormal sputum NOS

R0658 [D]Chest tightness

R06z. [D]Resp./chest symptoms-other

R06zz [D]Resp./chest symptoms NOS

R1531 [D]Positive culture - sputum

R2y1. [D]Respiratory failure

R2y10 [D]Cardiorespiratory failure

R2y1z [D]Respiratory failure NOS

SP132 Post operative chest infection

Appendix 5. The Read codes terms used to define inpatient admission.

Non-elective inpatient exacerbation events were defined as: Read codes 21, 22, 23, 24, 2A with the corresponding term: 'Admission Method Hospital Provider Spell' where the Primary or Secondary Diagnosis ICD-10 Code was one of:

J40 Bronchitis, not specified as acute or chronic

J42 Unspecified chronic bronchitis

J43 Emphysema

J44 Other chronic obstructive pulmonary disease

Emergency Department admission events were defined using the following codes (provided there was no recorded inpatient exacerbation event with an admission date of the same or the following date).

EM_Diagnosis_First,2 = '25' (i.e. related to any respiratory condition) or
EM_Diagnosis_Second_1,2 = '25'.

Appendix 6. GAD-7

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

(For office coding: Total Score T____ = ____ + ____ + ____)

Appendix 7. PHQ-9

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

Appendix 8. EQ5D and Health Thermometer

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

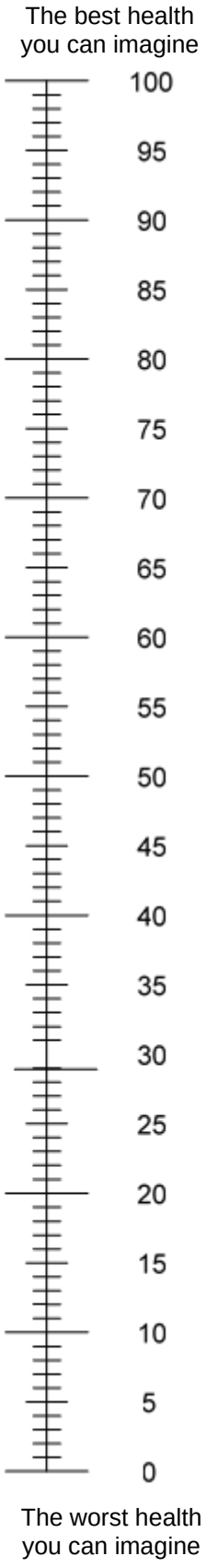
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



Appendix 9. Patient Information Leaflet: Intervention Arm

CLAHRC Wessex
Collaboration for Leadership in Applied Health Research and Care

NHS
National Institute for Health Research

Clinical And Social Characteristics And Demographics in Early COPD-CASCADE II

A study in Chronic Obstructive Pulmonary Disease (COPD) to establish if early, personalised medical review changes disease course.

Participant Information Sheet

You have expressed an interest in taking part in this research study which is being sponsored by the University of Southampton as part of the 'Collaboration for Leadership in Applied Health Research and Care' (CLAHRC Wessex). The purpose of this leaflet is to give you more information about why the research is being done and what taking part would mean. A summary of this study will also be available on a clinical trials register at http://clinicaltrials.gov.

Please ask us if anything is not clear or you would like more information. Take time to read this leaflet and decide whether or not you wish to take part. Part 1 tells you about why we are doing the study and the next steps if you choose to take part. Part 2 tells you about how the study is being conducted. One of our team will also talk through the leaflet with you before you make your final decision.

Thank you for reading.

PART1:

What is the purpose of the study?

The aim of this study is to identify Chronic Obstructive Pulmonary Disease (COPD) patients who currently have milder disease and to investigate whether a detailed, medical assessment which has time to assess all aspects of their care will improve their lung health and general wellbeing when compared to 'usual care' i.e. the care an individual with COPD would usually receive from their GP and practice nurse. There will be two groups of included in the study. One group will receive the detailed medical assessment from a respiratory doctor from Southampton General Hospital and one group will receive their usual care from their GP and practice nurse. We will monitor both groups over the course of a year to see if there is any difference in their lung health and general wellbeing. Patients from your GP practice are being invited to join the group receiving the detailed medical assessment by a respiratory doctor.

COPD is a condition resulting from lung damage, which, over time, causes individuals to suffer from symptoms including chronic cough and progressive breathlessness. In the UK, COPD is predominantly caused by cigarette smoking which may have occurred decades before the symptoms appear and the disease is diagnosed.

People with COPD, who have smoked in the past, are at higher risk of other medical problems such as heart disease and stroke. Being breathless and having multiple physical health problems can also lead to mental health problems such as anxiety and depression. This means it can be challenging to provide people with COPD enough time to fully assess and treat all their problems, particularly due to current pressure on the length of GP appointment times. This study investigates whether the solution to this problem may be allocating a block of time to see people with COPD routinely; early in their disease process, and ensuring if patients have these problems, they are being treated or prevented as thoroughly as possible. If this study shows a benefit to those people undergoing the detailed medical review it is something that, in the future, could potentially be included in the care of all patients with COPD.

Why have I been invited to participate in the study and what does it involve?

You have been invited to participate as:

- Your GP practice is one of the practices participating in the study
- You are on your GP Practice COPD Register i.e. you have a confirmed diagnosis of COPD
- Your answers to the COPD Assessment Test suggested the symptoms of COPD are affecting your life.

It is up to you to decide whether to join the study. If you chose to participate in the study you will be asked to attend the study site on three occasions over the period of a year. These visits include an initial enrolment visit, a follow up visit four to six weeks after this and a final visit twelve months after the initial visit. In addition, during the study time we will ask you to keep a record of any occasions where you have to take steroids or antibiotics for your chest.

What will happen during the study?

All the visits will take place either in your GP surgery or in space close to your GP surgery.

The initial visit will take about an hour and a half and we will ask you to take your inhalers as normal. If you have blue Salbutamol inhaler we would ask you to take it thirty minute before the appointment.

We will discuss the study risks and benefits in detail, answer any questions you might have and if you would like to take part we will ask you to sign a consent form which will include giving permission to access your electronic medical record at your GP Practice and giving permission for us to share any information we collect about you with your GP.

Do I have to take part?

Whether you decide to take part in the study is entirely up to you. If you do decide to take part you will need to sign the pages at the end of this leaflet to show you agree to participate in the study. This is called ‘giving consent’ and you should only do this if

1. A study staff member has explained the study to you
2. You understand the purpose of the study
3. You are willing to do what the study involves.

You should take as much time as you need to make up your mind. You can talk to your friends, family or GP to help you make a decision.

You can change your mind at any point in the study. You can leave the study at any point even if you have signed the form. You do not have to give a reason and it will not affect any care you receive from your GP, practice nurse, or any other NHS health professional.

What will I have to do if I decide to take part in the study?

At the first appointment, after you have given consent, the study doctor, who is a respiratory doctor from Southampton General Hospital, will ask you information about yourself and your disease including:

- How and when your COPD was diagnosed and what symptoms you currently have.
- Your medical history regarding any other problems or diseases you may have with you physical or mental health.
- Your medication and allergy history.
- Socio-demographic information i.e. your education, your work history, who makes up your household and whether you need any help with activities of daily living e.g. washing and shopping.

The study doctor will measure your lung function using breathing tests on a machine called a spirometer. These tests are similar to those you may have done with your practice nurse in your COPD Annual Review and are explained in more detail in the leaflet you received with your initial invitation letter from your GP practice.

You will undergo a general physical examination including measuring your height, weight, blood pressure and pulse rate. We will place a small clip over your finger, this is a painless procedure to measure your blood oxygen levels. The study doctor will also listen to your chest.

We will ask you to fill in four questionnaires about your physical and mental health and how COPD affects your life. You will be provided with a diary where you can make a note of any times you need steroids or antibiotics for your chest over the next year.

The study doctor will look at all aspects of your health and ensure that you are on the right treatment to keep you in the best health possible. If the study doctor feels you would benefit from any addition treatments or investigations these will be discussed with your GP and arranged. As with all medical treatments these are only recommendations and you do not have to take these recommendations up.

The second appointment with the study doctor will take place four to eight weeks after the first and will take approximately an hour. It will be a follow up appointment to the previous review to see how you are doing with any changes that might have been suggested in the previous appointment.

After this review, the study doctor may contact you by phone or by email if there are investigation results we need to let you know about or if you need any other input for your COPD.

The final appointment with the study team will take place approximately twelve months after the initial appointment and will take approximately an hour. This will involve reviewing the information in the diary you have kept and repeating the blowing tests (spirometry) and questionnaires. We will also look through your GP record to see how many times you have needed to use your GP service over the last year.

Throughout the study you will still have access to your GP and practice nurse as normal and all information you give to the study doctor will be shared with your GP.

How will being part of this study affect my lifestyle?

You will need to have the time and transport to be able to attend the three study appointments. It could be that the study doctor recommends additional investigations or treatments which might require more time and transport.

You will need to fill in the diary we give you each time you take steroid or antibiotics for your chest.

What are my alternatives to taking part in the study?

You can choose to continue to receive your normal care from your GP and practice nurse. Whether or not you choose to take part in the study does not alter how you can access your GP, practice nurse or any other health professional.

What side effects or risks can I expect from the study?

When you are participating in spirometry you will need to have taken you blue (salbutamol) inhaler. If you do not have one of these then one will be provided by the study team. Allergic reactions to salbutamol and possible side effects (shakiness, increased heart rate, headaches) are rare and should go away within several minutes.

Some of the questionnaires deal with how you feel about your life. Occasionally, if people are feeling down or depressed, they can find this upsetting. If this is the case we could talk to you about this is more detail at the time or we can make an appointment for you to talk to your GP or Practice nurse if you would prefer.

What are the possible benefits of taking part?

Taking part in this study may not have a direct benefit for you.

Some possible benefits to you are:

- The study doctor is a respiratory doctor so you will receive specialist review of your COPD.
- The study doctor may be able to adapt your treatment to better suit your disease

Whether or not you choose to take part in the study, all patients with COPD in your GP practice will be invited to attend a patient education session to learn more about COPD at the end of the study period.

What happens when the research study stops?

You will continue to access your GP practice as normal during the study, so when the study finishes your care will continue as normal with your GP and practice nurse. The results of the study will be sent to you in the form of a summary sheet as well as being available on the CLAHRC website.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about your participation will be kept confidential.

What if there is a problem?

You can contact the study doctor Dr Lucy Rigge or study nurses Mrs Kate Lippiett and Mrs Kate Gillett about any questions or concerns you have about the study on:

07833482100 or UHS.COPDstudy@nhs.net

PART 2

Do I have to stay in the study?

You may choose to leave the study at any time, without giving a reason. Please call or email the study doctor or nurse if you change your mind and decide you no, longer wish to participate. This will not affect your future medical care.

We may ask you to leave the study if:

- You find cannot understand or follow instructions for follow up visits
- The study doctor thinks it is in your best interests to stop.

What happens if I leave the study?

No more information about you will be collected. Any information you gave us before you left the study will still be used.

What if there is a problem?

If you have a concern about any aspect of this study, you can speak to the study researchers on 07833482100 or UHS.COPDstudy@nhs.net who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do so via the NHS Complaints Procedure. Details can be obtained from INVOLVE a government funded organization to support active public involvement in NHS research. INVOLVE can be contacted on 02380 651088 or at admin@invo.org.uk.

Any concerns can also be raised to the University of Southampton on 02380595058 or at rgoinfo@soton.ac.uk.

Will my information be kept private?

Personal information about you such as your name and address will be kept confidential and kept in a secure file that can only be accessed by members of the study team. Your study information will be labelled with a code number which will not include your name or address so will not identify you. The study team will be free to use this coded information in publications such as journal articles to share the results of the study with other doctors, health professionals and members of the public to try to better understand COPD, other diseases and conditions. Neither you, nor your GP surgery would be named in any publication.

Sometimes government, hospital or university officials check to see research studies are being run properly. Your study information may also be checked by these people, they will keep all information confidential.

Your personal information will be kept for ten years in accordance with policy of the University of Southampton. After this time it will be destroyed in a secure manner.

Who is organising and funding the research?

The research is funded by the Wessex CLAHRC- this is a government funded, five year research and implementation programme with the aim of improving the health of the people of Wessex.

Who has reviewed the research?

All research in the NHS is reviewed by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed by the Wessex CLAHRC and approved for conduct in the NHS by the National Research and Ethics Committee.

NHS
National Institute for Health Research

CONSENT FORM

Title of Project: **C**linical **A**nd **S**ocial **C**haracteristics **A**nd **D**emographics in **E**arly **COPD**- **CASCADE II**

Name of Researcher:

Please initial box

1. I confirm that I have read and understand the information sheet dated 02/07/2015 (version 2) 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 regulatory authorities or from the University of Southampton, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

4. I agree to my GP being informed of my participation in the study.

5. I agree to take part in the above study.

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 for GP notes

Appendix 10. Patient Information Leaflet: Control Arm

CLAHRC Wessex
Collaboration for Leadership in Applied Health Research and Care

NHS
National Institute for Health Research

Clinical And Social Characteristics And Demographics in Early COPD-CASCADE II

A study in Chronic Obstructive Pulmonary Disease (COPD) to establish if early, personalised medical review changes disease course.

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Please ask us if anything is not clear or you would like more information. Take time to read this leaflet and decide whether or not you wish to take part. Part 1 tells you about why we are doing the study and the next steps if you choose to take part. Part 2 tells you about how the study is being conducted. One of our team will also talk through the leaflet with you before you make your final decision.

Thank you for reading.

PART1:

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The aim of this study is to identify Chronic Obstructive Pulmonary Disease COPD patients who currently have milder disease and to investigate whether a detailed, medical assessment which has time to assess all aspects of their care will improve their lung health and general wellbeing when compared to 'usual care' i.e. the care an individual with COPD would usually received from their GP and practice nurse. There will be two groups of included in the study. One group will receive the detailed medical assessment from a respiratory doctor from Southampton General Hospital and one group will receive their usual care from their GP and practice nurse. We will monitor both groups over the course of a year to see if there is any difference in their lung health and general wellbeing. Patients from your GP practice are being invited to join the group receiving 'usual care' from your GP and practice nurse.

COPD is a condition resulting from lung damage, which, over time, causes individuals to suffer from symptoms including chronic cough and progressive breathlessness. In the UK, COPD is predominantly caused by cigarette smoking which may have occurred decades before the symptoms appear and the disease is diagnosed.

People with COPD, who have smoked in the past, are at higher risk of other medical problems such as heart disease and stroke. Being breathless and having multiple physical health problems can also lead to mental health problems such as anxiety and depression. This means it can be challenging to provide people with COPD enough time to fully assess and treat all their problems, particularly due to current pressure on the length of GP appointment times. This study investigates whether the solution to this problem may be allocating a block of time to see people with COPD routinely; early in their disease process, and ensuring if patients have these problems, they are being treated or prevented as thoroughly as possible. If this study shows a benefit to those people undergoing the detailed medical review it is something that, in the future, could potentially be included in the care of all patients with COPD.

Why have I been invited to participate in the study and what does it involve?

You have been invited to participate as:

- Your GP practice is one of the practices participating in the study
- You are on your GP Practice COPD Register i.e. you have a confirmed diagnosis of COPD
- Your answers to the COPD Assessment Test suggested the symptoms of COPD are affecting your life.

It is up to you whether to decide to join the study. If you chose to participate in the study you will be asked to attend the study site on two occasions over the period of a year. These visits include an initial enrolment visit and a final visit twelve months after the initial visit. In addition, during the study time we will ask you to keep a record of any occasions where you have to take steroids or antibiotics for your chest.

What will happen during the study?

All the visits will take place either in your GP surgery or in space close to your GP surgery.

The initial visit will take about an hour and we will ask you to take your inhalers as normal. If you have blue Salbutamol inhaler we would ask you to take it thirty minute before the appointment.

We will discuss the study risks and benefits in detail, answer any questions you might have and if you would like to take part we will ask you to sign a consent form which will include giving permission to access your electronic medical record at your GP Practice and giving permission for us to share any information we collect about you with your GP.

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4. A study staff member has explained the study to you
5. You understand the purpose of the study
6. You are willing to do what the study involves.

You should take as much time as you need to make up your mind. You can talk to your friends, family or GP to help you make a decision.

You can change your mind at any point in the study. You can leave the study at any point even if you have signed the form. You do not have to give a reason and it will not affect any care you receive from your GP, practice nurse, or any other NHS health professional.

What will I have to do if I decide to take part in the study?

At the first appointment, after you have given consent, the study nurse will ask you information about yourself and your disease including:

- How and when your COPD was diagnosed and what symptoms you currently have.
- Your medical history regarding any other problems or diseases you may have with you physical or mental health.
- Your medication and allergy history.
- Socio-demographic information i.e. your education, your work history, who makes up your household and whether you need any help with activities of daily living e.g. washing and shopping.

The study nurse will measure your lung function using breathing tests on a machine called a spirometer. These tests are similar to those you may have done with your Practice Nurse in your COPD Annual Review and are explained in more detail in the leaflet you received with your initial invitation letter from your GP practice.

You will undergo a general physical examination including measuring your height, weight, blood pressure and pulse rate.

We will ask you to fill in four questionnaires about your physical and mental health and how COPD affects your life. You will be provided with a diary where you can make a note of any times you need steroids or antibiotics for your chest over the next year.

The final appointment with the study team will take place approximately twelve months after the initial appointment and will take approximately an hour. This will involve reviewing the information in the diary you have kept and repeating the blowing tests (spirometry) and questionnaires. We will also look through your GP record to see how many times you have needed to use your GP service over the last year.

Throughout the study you will still have access to your GP and practice nurse as normal and all information you give to the study doctor will be shared with your GP.

How will being part of this study affect my lifestyle?

You will need to have the time and transport to be able to attend the two study appointments.

You will need to fill in the diary we give you each time you take steroid or antibiotics for your chest.

What are my alternatives to taking part in the study?

You can choose to continue to receive your normal care from your GP and practice nurse. Whether or not you choose to take part in the study does not alter how you can access your GP, practice nurse or any other health professional.

What side effects or risks can I expect from the study?

When you are participating in spirometry you will need to have taken you blue (salbutamol) inhaler. If you do not have one of these then one will be provided by the study team. Allergic reactions to salbutamol and possible side effects (shakiness, increased heart rate, headaches) are rare and should go away within several minutes.

Some of the questionnaires deal with how you feel about your life. Occasionally, if people are feeling down or depressed, they can find this upsetting. If this is the case we can make an appointment for you to talk in more detail to your GP or Practice nurse.

What are the possible benefits of taking part?

Taking part in this study may not have a direct benefit for you. The results of the study may help doctors learn more about COPD and this may help future patients.

Whether or not you choose to take part in the study, all patients with COPD in your GP practice will be invited to attend a patient education session to learn more about COPD at the end of the study period.

What happens when the research study stops?

You will continue to access your GP practice as normal during the study, so when the study finishes your care will continue as normal with your GP and practice nurse. The results of the study will be sent to you in the form of a summary sheet as well as being available on the CLAHRC website.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about your participation will be kept confidential.

What if there is a problem?

You can contact the study doctor Dr Lucy Rigge or study nurses Mrs Kate Lippiett and Mrs Kate Gillett about any questions or concerns you have about the study on:

07833482100 or UHS.COPDstudy@nhs.net

PART 2

Do I have to stay in the study?

You may choose to leave the study at any time, without giving a reason. Please call or email the study doctor or nurse if you change your mind and decide you no, longer wish to participate. This will not affect your future medical care.

We may ask you leave the study if:

- You find cannot understand or follow instructions for follow up visits
- The study doctor thinks it is in your best interests to stop.

What happens if I leave the study?

No more information about you will be collected. Any information you gave us before you left the study will still be used.

What if there is a problem?

If you have a concern about any aspect of this study, you can speak to the study researchers on 07833482100 or UHS.COPDstudy@nhs.net who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do so via the NHS Complaints Procedure. Details can be obtained from INVOLVE a government funded organization to support active public involvement in NHS research. INVOLVE can be contacted on 02380 651088 or at admin@invo.org.uk.

Any concerns can also be raised to the University of Southampton on 02380595058 or at rgoinfo@soton.ac.uk.

Will my information be kept private?

Personal information about you such as your name and address will be kept confidential and kept in a secure file that can only be accessed by members of the study team. Your study information will be labelled with a code number which will not include your name or address so will not identify you. The study team will be free to use this coded information in publications such as journal articles to share the results of the study with other doctors, health professionals and members of the public to try to better understand COPD, other diseases and conditions. Neither you, nor your GP surgery would be named in any publication.

Sometimes government, hospital or university officials check to see research studies are being run properly. Your study information may also be checked by these people, they will keep all information confidential.

Your personal information will be kept for ten years in accordance with policy of the University of Southampton. After this time it will be destroyed in a secure manner.

Who is organising and funding the research?

The research is funded by the Wessex CLAHRC- this is a government funded, five year research and implementation programme with the aim of improving the health of the people of Wessex.

Who has reviewed the research?

All research in the NHS is reviewed by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed by the Wessex CLAHRC and approved for conduct in the NHS by the National Research and Ethics Committee.

NHS
National Institute for Health Research

CONSENT FORM

Title of Project: **C**linical **A**nd **S**ocial **C**haracteristics **A**nd **D**emographics in **E**arly **COPD**-**CASCADE II**

Name of Researcher:

Please initial box

1. I confirm that I have read and understand the information sheet dated 02/07/2015 (version 2) 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 regulatory authorities or from the
University of Southampton, where it is relevant to my taking part in this research.
I give permission for these individuals to have access to my records.

4. I agree to my GP being informed of my participation in the study.

5. I agree to take part in the above study.

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 for GP notes

Appendix 11. Exacerbation Diary

Exacerbation Diary:

In this diary please record the following:

- Each time you take a course of antibiotics for your COPD.
    - In the 'antibiotic' column please write;
        - The date the course was started.
        - The date it finished.
        - Who prescribed it e.g. GP, practice nurse, A&E or out of hours GP. If you took your stand-by or 'just in case' medications you keep at home please write 'stand by'.
- Each time you take a course of steroids (prednisolone) for your COPD.
    - In the 'steroid' column please write;
        - The date the course was started.
        - The date it finished.
        - Who prescribed it e.g. GP, practice nurse, A&E or out of hours GP. If you took your stand-by or 'just in case' medications you keep at home please write 'stand by'.

If you run out of diary sheets either call us on 07833482100 or email us on UHS.COPDstudy@nhs.net

Date	Antibiotic course -Please record the date the course was started and the date it was completed. -Please record who prescribed the course e.g. GP, Practice Nurse, A&E, Out of hours GP or if they were standby medications.	Steroid course -Please record the date the course was started and the date it was completed. -Please record who prescribed the course e.g. GP, Practice Nurse, A&E, Out of hours GP or if they were standby medications.
Example: *26th August 2015*	*My GP prescribed antibiotics 26/8/15- 2/9/15*	*My GP prescribed steroid 26/8/15- 2/9/15*

Appendix 12. Intervention Arm Initial Appointment Source Document

Initial (time point 0) proforma- intervention arm: source document				
Patient number:			**Contact number:**	
Address:				
DOB	**Age**	**Gender**	**Ethnicity**	
Height (m)	**Weight (kg)**		**BMI**	
COPD history				
COPD diagnosis confirmed?				
Dementia	**MMSE**	**Osteoporosis**	**Sinus disease**	**Ischaemic Heart Disease**
Left heart failure	**Cor pulmonale**	**Asthma**	**Bronchiectasis**	**Pulmonary Fibrosis**
Hypertension	**Anxiety**	**Depression**	**Diabetes**	**Hyperlipidaemia**
Gastro-oesophageal reflux	**Obstructive sleep apnoea**	**Raised eosinophil/neutrophil ratio**	**Pneumonia**	
Other Past Medical History				
Smoking status (GP)?	**Smoking status (pt)**	**Ex-smoker?**	**Start date:**	**Quit date**
Pack years:	**Smoked tobacco only?**	**Other smoking history**		
mMRC score (GP):	**mMRC score (pt)**		**Exacerbations in previous year (pt):**	**Exacerbations in last year (GP):**
Spirometry contraindications checked?				
Pulse	**BP**		**Oxygen Saturations**	
Spirometry (pre-bronchodilator):				
FEV1 (l):	**FEV1 %:**	**FVC (l):**	**FVC %:**	**Ratio:**
Spirometry (post bronchodilator):				
FEV1 (l):	**FEV1 %:**	**FVC (l):**	**FVC %:**	**Ratio:**
Drug history (GP)		**Drug history (pt)**		**Allergies/atopy:**
				Alcohol history
Occupational history:				
TB:	**Asbestos:**	**Pets:**		
Schooling level:		**Lives alone?**		
Mobility?		**Independent with ADLS?**		

Exercise tolerance at own pace on flat			
CAT	**GAD**	**PHQ-9**	**EuroQol**
DOSE (GP):		**DOSE (pt):**	
Examination: **Inhaler technique:**			
Impression:			
Plan: **Pulmonary Rehab:** **Diet:** **Smoking:** **Inhalers:** **Oxygen requirements:** **Mental Health Requirements:** **Social Requirements:** **Cormorbidity Requirements:** **Secondary Prevention Requirements:** **Investigations:** **Care contact and exacerbation diary:** **Education required- what is COPD?** **-exacerbations** **-standby meds** **Onward referrals:**			

Appendix 13. Education Session Invite

CLAHRC Wessex
Collaboration for Leadership in Applied Health Research and Care

NHS National Institute for Health Research

Clinical **A**nd **S**ocial **C**haracteristics **A**nd **D**emographics in **E**arly **COPD**-**CASCADE II**

A study in Chronic Obstructive Pulmonary Disease (COPD) to establish if early, personalised medical review changes disease course.

We would like to *thank you* for taking part in CASCADE II- the COPD research study. Without people like yourself giving up your time we would not be able to move on with research to improve the treatment and care of people with lung problems.

As a small *'thank you'* we would like to invite you to an education session especially for people with COPD. During the session, one of the study team will talk about ways to set yourself health goals when you have COPD. There will also be the opportunity to ask questions of our team nurses and doctors.

Two sessions will be taking place and you are welcome to attend either. Please feel free to bring any interested family members or Carers.

Tea and coffee will be provided.

The sessions will take place on:

Monday 10th October 2016 from 09.30-11.30

At The Guide Centre

Timsbury Drive, Maybush, Southampton SO16 4EQ

or

Wednesday 12th October from 1.30-3.30

At Bitterne Health Centre

Commercial St, Southampton SO18 6BT

There is limited free parking available at both venues.

Dr Lucy Rigge (Principal Investigator)

Appendix 14. Participant Feedback Form.

CLAHRC Wessex
Collaboration for Leadership in Applied Health Research and Care

NHS National Institute for Health Research

Participant feedback for CASCADE II

COPD study led by Dr Lucy Rigge

Thank you for taking part in our study. We would be very grateful for your feedback regarding your experience to help guide us in designing research studies in the future. Please note all feedback is anonymous.

1. What effect has taking part in the study had on your lung health?

Very Positive | Positive | No effect | Negative | Very Negative

If you said the study had a positive or negative effect on your lung health, could you tell us a little more about what this was?

_____

_____

_____

_____

2. What effect has taking part in the study had on your general health?

Very Positive | Positive | No effect | Negative | Very Negative

If you said the study had a positive or negative effect on your general health, could you tell us a little more about what this was?

_____

_____

_____

_____

3. Please tell us how important the following things were to you whilst you were participating

Important | Not important

i) The study location being in your GP surgery

ii) Being able to see a lung expert

iii) Good communication between the visiting Dr and your GP

iv) Being about to talk about all your concerns

4. Can you tell us anything else you liked about the study:

_____

_____

_____

_____

CLAHRC Wessex
Collaboration for Leadership in Applied Health Research and Care

NHS
National Institute for Health Research

5. Can you tell us about anything you think we could have done better?

6. Do you have any other comments or feedback about the study?

Thank you for taking the time to share your views.

Please return the form to the study team in the enveloped provided.

Appendix 15. Table showing baseline distribution of CAT score components between the Intervention and Control arms.

Symptom scores at Baseline	Control arm (N=44)	Intervention arm (N=76)
Cough		
I never cough 0	0 (0%)	1 (1.3%)
1	8 (18.2%)	10 (13.2%)
2	14 (31.8%)	20 (26.3%)
3	12 (27.3%)	29 (38.2%)
4	7 (15.9%)	13 (17.1%)
I cough all the time 5	3 (6.8%)	3 (3.9%)
Phlegm		
I have no phlegm in my chest 0	3 (6.8%)	6 (7.9%)
1	6 (13.6%)	10 (13.2%)
2	14 (31.8%)	16 (21.1%)
3	13 (29.5%)	26 (34.2%)
4	8 (18.2%)	15 (19.7%)
My chest is completely full of phlegm 5	0 (0%)	3 (3.9%)
Tight chest		
My chest does not feel tight at all 0	5 (11.4%)	10 (13.2%)
1	9 (20.5%)	10 (13.2%)
2	13 (29.5%)	23 (30.3%)
3	13 (29.5%)	20 (26.3%)
4	3 (6.8%)	9 (11.8%)
My chest feels very tight 5	1 (2.3%)	4 (5.3%)
Breathlessness		
I am not breathless when I walk up 0	0 (0%)	0 (0%)
one flight of stairs 1	2 (4.5%)	3 (3.9%)
2	9 (20.5%)	9 (11.8%)
3	9 (20.5%)	18 (27.9%)
When I walk up one flight of stairs I 4	15 (34.1%)	23 (30.3%)
am very breathless 5	9 (20.5%)	23 (30.3%)
Activity		
I am not limited doing any activities 0	7 (15.9%)	12 (15.8%)
1	5 (11.4%)	14 (18.4%)
2	7 (15.9%)	16 (21.1%)
3	18 (40.9%)	13 (17.1%)
4	5 (11.4%)	13 (17.1%)
I am very limited doing any activities 5	2 (4.5%)	8 (10.5%)

Symptom scores at Baseline	Control arm (N=44)	Intervention arm (N=76)
Confidence		
I am confident leaving my home 0	14 (31.8%)	35 (46.1%)
1	13 (29.5%)	8 (10.5%)
2	5 (11.4%)	13 (17.1%)
3	8 (18.2%)	12 (15.8%)
4	3 (6.8%)	5 (6.6%)
I am not confident leaving my home 5	1 (2.3%)	3 (3.9%)
Sleep		
I sleep soundly 0	12 (27.3%)	18 (23.7%)
1	7 (15.9%)	14 (18.4%)
2	6 (13.6%)	12 (15.8%)
3	13 (29.5%)	15 (19.7%)
4	4 (9.1%)	11 (14.5%)
I do not sleep soundly 5	2 (4.5%)	6 (7.9%)
Energy		
I have lots of energy 0	0 (0.0%)	2 (2.6%)
1	2 (4.5%)	7 (9.2%)
2	9 (20.5%)	21 (27.6%)
3	17 (38.6%)	24 (31.6%)
4	12 (27.3%)	12 (15.8%)
I have no energy at all 5	4 (9.1%)	10 (13.2%)

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