Swansea University
Prifysgol Abertawe

S*T*ep D*OW*n Inh*A*lers in the *R*eal Worl*D* (TOWARD): a feasibility study

Joseph Alexander Annandale

Submitted to Swansea University in fulfilment of the requirements for the Degree of Medical and Health Care Studies MSc by Research

Swansea University 2023

ABSTRACT

INTRODUCTION

Current clinical guidelines recommend the use of inhaler corticosteroids (ICS) in combination with long-acting bronchodilators in the management of chronic obstructive pulmonary disease (COPD). Despite their use being recommended in patients who exacerbate frequently, in practice they are more broadly prescribed potentially exposing patients to side effects but little or no benefit with a cost burden. Randomised studies with strict inclusion/exclusion criteria have demonstrated it is possible to safely stop an ICS. This feasibility study aimed to test a real-world protocol to stop ICS in patients with stable COPD, despite having the typical exclusion criteria seen in the randomised studies.

METHODS

Stable participants with a confirmed diagnosis of COPD who were prescribed ICS as well as 2 long-acting bronchodilators were recruited. Those with an exacerbation within six weeks, a history of asthma or peripheral blood eosinophil count >600 dl/l were excluded. Participants were shown the four currently licensed dual long-acting bronchodilators combination inhalers and were asked to select one. After confirming effective inhaler technique, they were prescribed the combination inhaler. Participants were free to restart an ICS at any point. Lung function (FEV_1) and quality of life scores (CAT) were recorded at baseline, 4 and 52-week visits. Exacerbations requiring treatment were compared 12 months pre and post inhaler switch. Feasibility was measured using a Model with predefined criteria.

RESULTS

Of the 10 feasibility criteria 60% were met (participant follow up/completion; data collection, primary care access; cost savings) and 40% not met (recruitment targets; primary care staff participation; numbers completing study not on an ICS; exacerbation rates). 3 participants died within the study period but none attributed to their participation.

57% (n=37) of participants did not restart an ICS and there was no significant rise in exacerbation rates when compared to the 12 months prior to the study (p=0.229). There was an increase in hospital admission rate but still very low from 0.05/year to 0.2/year (p=0.007). There was no significant change in FEV1 (p=0.883) or CAT scores (p=0.662). Overall prescribing cost savings were significant and estimated at >£18K (p=<0.001). Analysis by outcome (those completing study on ICS and those not) demonstrated a clear difference in the

groups at baseline with those not restarting an ICS having less exacerbations in the 12 months prior to the study with better lung function and quality of life.

DISCUSSION

The results suggest that overall, the study protocols were safe with the potential to discontinue ICS therapy in some patients. The clear differences within the group at baseline may account for those needing to restart ICS therapy and appears those with more severe disease continued the decline in terms of exacerbations, lung function, quality of life and hospital admissions. These factors could be considered and potentially result in amendments to the study protocol for a future larger study. A larger study would be feasible but recruitment targets would need to be re-evaluated and who delivers the intervention considered, as Primary Care have no capacity to directly support such a study.

DECLARATION

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

Signed.....[redacted].....

Date.....26/1/23.....

This thesis is the result of my own investigations, except where otherwise stated. Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

Signed.....[redacted].....

Date.....26/1/23.....

I hereby give consent for my thesis, if accepted, to be available for photocopying and for inter-library loan, and for the title and summary to be made available to outside organisations.

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Date.....26/1/23.....

The University's ethical procedures have been followed and, where appropriate, that ethical approval has been granted.

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ACKNOWLEDGEMENTS

I would like to thank my supervisors, Prof. Keir Lewis and Prof. Hayley Hutchings as without their guidance, patience and support I'd have not had the opportunity to undertake and complete this work. I'd also like to thank Dr Gareth Davies for his statistical advice.

I have to thank Sarah Rees who organised me and supported the study – without her the study would not have run so smoothly. Also, Dr Rachel Gemine who was always there for advice and support.

Hywel Dda University Health Board were very supportive, as were my colleagues, managers and the Research and Development Department - all were crucial so thank you all. I'm also thankful for the support of our local GP practices.

I must acknowledge Health and Care Research Wales as without the award of a Clinical Research Time Award which paid for my time and clinical backfill this study would not have been possible. Thanks to the Association of Respiratory Nurse Specialists and the Burdett Trust for Nursing for their grants.

Without the support of our patient population no study would be possible and working with them was an honour and always a pleasure.

Finally, my family's support kept me going when at my lowest, so a special thanks to my wife Helen and daughters Ffion and Cerys.

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LIST OF ABBREVIATIONS

AC - Adenylyl cyclase
ARNS – Association of Respiratory Nurse Specialists
ARTP - Association for Respiratory Technology and Physiology
BDP - Beclomethasone dipropionate
BMI – Body mass index
BODE – Body mass index, obstruction, dyspnoea, exercise capacity
BLF – British Lung Foundation
CAT – COPD assessment test
CPRD - Clinical Practice Research Datalink
CAP – Community acquired pneumonia
CI – Confidence interval
COSH – Control of substances hazardous to health
COPD – Chronic obstructive pulmonary disease
CRQ – Chronic respiratory disease questionnaire
cAMP - Cyclic adenosine monophosphate
DALYs – Disability adjusted life years
DPI – Dry powder inhaler
ESCAPE - European Study of Cohorts for Air Pollution Effects
EU – European Union
EQ-5D - EuroQol-5D health related quality of life questionnaire
ECO – Exhaled carbon monoxide
FEV_1 – Forced expiratory volume in 1 second
FVC – Forced vital capacity
GP – General Practice
GFE - Glucocorticoid response element
GOLD – Global Initiative for Obstructive Lung Disease
HR – Hazard ratio
HCRW – Health and Care Research Wales
HSE - Health and Safety Executive
HTA – Health Technology Assessment
HES - Hospital Episode Statistics

ICS – Inhaled corticosteroids
IL – Interleukin
JVP - Jugular venous pressure
LAMA – Long-acting muscarinic antagonist
LABA – Long-acting beta receptor agonist
LLN - Lower limit of normal
LTOT – Long term oxygen therapy
LSUT - Lung Screen Update Trial
LVRS – Lung volume reduction surgery
MRC – Medical Research Council
MUR – Medicines use review
MMAS-8 - Morisky Medication Adherence Scale
M receptors - Muscarinic cholinergic receptors
MITT - multiple inhaler triple therapy
NIHR – National Institute for Health Care Research
NO_2 – Nitrogen dioxide
NOTT - Nocturnal Oxygen Therapy Trial Group
NIV – Non-invasive ventilation
NVDI - Normalised vegetation difference index
NNT – Numbers needed to treat
$PaCO_2$ – Partial pressure of arterial carbon dioxide
PaO_2 – Partial pressure of arterial oxygen
PDE4 - Phosphodiesterase-4 inhibitors
PPV - Pneumococcal polysaccharide vaccine
pMDI - Pressurised metered dose inhalers
PRISm – Preserved Ratio Impaired Spirometry
PDC – Proportion of days covered
PKA - Protein kinase A
PAP – Pulmonary artery pressure
QoL – Quality of life
RCT – Randomised controlled trail
REC – Research Ethics Committee

RNS – Respiratory Nurse Specialist
SF-36 - Medical Short form 36 questionnaire
SABA – Short acting beta agonist
SITT - Single inhaler triple therapy
SGRQ – St George's Respiratory Questionnaire
TDI - Transition dyspnoea index
TOWARD - sTep dOWn inhalers in the reAl world
UK – United Kingdom
US – United States of America
VAS – Visual analogue scale
WHO – World Health Organisation

PUBLICATIONS / PRESENTATIONS PAGE / PRIZES

Presentation: sTep dOWn inhAlers in the Real worlD (TOWARD): Early feasibility results. Welsh Thoracic Society Annual Conference October 2017 Aberavon

Presentation: sTep dOWn inhAlers in the Real worlD (TOWARD): Early feasibility results. Study advisory board February 2018 Cardiff

Poster presentation: sTep dOWn inhAlers in the Real worlD (TOWARD): Patient choices of LABA/LAMA devices in the real world. Association of Respiratory Nurse Specialists Annual Conference May 2018

Spoken Poster Session Winner: sTep dOWn inhAlers in the Real worlD (TOWARD): Patient choices of LABA/LAMA devices in the real world. Association of Respiratory Nurse Specialists Annual Conference May 2018

Poster presentation: sTep dOWn inhalers in the reAl woRlD (TOWARD) Patient choices of LABA/LAMA devices and their potential prescribing cost savings. Swansea University Medical School Postgraduate Conference May 2018

Poster presentation: Does patient choice improve adherence to COPD inhalers? Association of Respiratory Nurse Specialists Annual Conference May 2019

1st Prize Poster presentation: Does patient choice improve adherence to COPD inhalers? Association of Respiratory Nurse Specialists Annual Conference May 2019

Presentation: sTep dOWn inhalers in the reAl WoRlD (TOWARD): A feasibility study Welsh Thoracic Society Annual Conference October 2019 Llanelli

CHAPTER 1: BACKGROUND AND INTRODUCTION

1.1 Why did I attempt this Research?

I have been a Respiratory Nurse Specialist (RNS) at Prince Philip Hospital for nearly 27 years. This role has been predominantly within a secondary care setting. I run nurse-led clinics with inpatient work and supervise other RNSs. We work closely with general nursing staff, medical staff, physiologists, allied health professionals and managers to deliver respiratory care to the people of Hywel Dda and Wales. Other key parts of my role include teaching and training a wide range of health professionals (including doctors, physician associates, nurses, health care assistants, and physiologists), medical and nursing students and the pharmaceutical industry. I have a special interest in airways disease and non-invasive ventilation (NIV). I also lead on service development and enjoy research.

My involvement in research goes back 20 years, having developed these skills to the point that I had the desire and skills to take more of a lead role. I've enjoyed co-authoring then led authoring review articles and original papers, book chapters and have presented at local, national and international conferences.

I continue to be active within national organisations such as The British Thoracic Society and The Association of Respiratory Nurse Specialist (ARNS) previously being a member the of Research and Education Sub-group, guideline development groups and previously Standards of Care Committee. These opportunities have allowed me to develop key skills such as critical thinking and evidence review which has ignited my interest and desire to answer key clinical questions through research.

I successfully gained a 3-year Clinical Research Time Award in 2017 from Health and Care Research Wales (HCRW). This highly competitive grant supported this work and other research activity including being the local principal investigator (PI) on 3 national research studies. I was also supported by grants from the Association of Respiratory Nurse Specialists (ARNS) and the Burdett Trust for Nursing.

I'm passionate about respiratory health with a focus on clinical practice and patients. When I started in this role, Chronic Obstructive Pulmonary Disease (COPD) was the Cinderella condition compared to higher profile conditions such as asthma but it has gained in clinical and research prominence over the last 20 years.

The early clinical focus on asthma (1950s-1990s) and lack of evidence around diagnosing and treating COPD I believe has contributed to significant overlap and confusion in diagnosis and treatment of the two conditions. This will become more apparent later in relation to the use of inhaled corticosteroids (ICS). Probably the moment I still recall that my interest in COPD really became evident was when I was fortunate to hear the late Dr Tim Griffiths present his work and research on pulmonary rehabilitation for COPD in Cardiff. This made me realise the real impact of this disease on patients and that our attitudes as health professionals often did not help; in that we can do far more to help them and empower them through education and co-production.

The study in my thesis is designed to try answer an important and relevant clinical question but also to align closely with the 4 principles of Prudent Healthcare.(1-3) This feasibility study reflects every day 'real world' practice, better representing the COPD populations attending district general hospitals rather than highly selected groups enrolled in traditional randomised controlled trials. I was struck by the selection bias in major studies: a retrospective analysis of 893 patients on a large British primary care database against multiple COPD studies' inclusion/exclusion criteria, concluded the median eligibility was 24% for all studies but as low as 3.5% for studies requiring a history of exacerbations.(4)

1.2 My role in the study

Being the Principal Investigator (PI) I led this open label, non-randomised, 12-month, observational feasibility study, testing an inhaled corticosteroid (ICS) withdrawal protocol. We placed patient's own selection of the alternative inhalers available, at the centre of the switching process, rather than a clinician deciding what they thought the best inhaler device would be for that patient. We followed 66 participants, recording numbers willing to switch inhalers and the number maintained off ICS. We recorded clinical outcomes, but also safety, cost-savings and explored the practical issues of implementing ICS-stopping at scale. I explored the reasons for patient device preference and if there was an association between inhaler device choice and future inhaler treatment adherence/usage. I led on study design, applying for local Ethics Committee approval in 2017 (17/WA/0009), I made the suggested amendments needed for approval as well as subsequent major amendments. I attended the Joint Clinical Research Faculty in 2017 at Swansea University for Research and Development (R&D) approval and made amendments following this. I led screening for

study inclusion within the hospital and primary care settings and was the sole recruiter, undertaking all the clinical assessments at all time-points personally. I built the study databases and led on data entry. The study went through an internal audit within Hywel Dda R&D in 2019 and I actioned and corrected the minor issues raised. I undertook all the statistical analysis with guidance from a statistician. I presented various results at a number of local, Welsh and national conferences, winning Best Poster presentation prizes twice. I was fortunate to be supported by a number of very experienced researchers.

There were challenges in completing this work. Initially I found the approval process frustrating by the number of different organisations and order of the approvals process which seemed to take longer than anticipated. Fortunately, having the help and support of experienced researchers was invaluable. Recruitment was a challenge, after the initial surge it slowed down and although local Primary Care Practices were supportive in allowing access to their patient populations and accommodation, they were unable to commit any staff to support the study leaving all the clinical input to be undertaken by the PI.

As part of the CRT award, I was actively involved in a wider research programme and needed to support other studies. On reflection, there were times I may have focused too much on these, slowing down the study progress. Not having any real skill in statistical analysis was a challenge but with the support of statisticians, experienced researchers, attending University courses and good old-fashioned books so in the end felt confident and competent in the outcomes.

The challenges I encountered included time allocation during a busy NHS job following the ending of my protected time from the CRT award. This coincided with the COVID outbreak, with its focus on respiratory care and the need for respiratory specialists on the front line. My main supervisor was the COVID lead and working within COVID restricted area, so I lost direct access to him as I was working in a different area. Although we had recruited all patients, the follow ups were compromised by lockdown, room and staff availability and understandable patient concerns about attending hospitals. Post pandemic I struggled to dedicate time to the thesis during NHS start up.

Motivation was difficult post pandemic, finding it difficult not to reflect on the impact it had on me personally, family and colleagues – I decide to prioritise any spare time with family and a better work/life balance. This change of focus led to the reluctant but carefully considered decision to downgrade and was agreed with supervisors.

1.3 Thesis outline

Initially the aim is to provide a broad background as to what COPD is, looking at it causes and prevalence. Causes of the increasing mortality rates will be explored as well as the high levels of morbidity. Correct and early diagnosis is important and described as well as the impact of exacerbations, a key outcome within the main study. Treatments are available but adherence to key treatments are poor, adherence being one of the outcomes within the main study.

Treatments can be both non-pharmacological and pharmacological. Primary and secondary prevention is important and discussed particularly in relation to smoking, smoking cessation and occupational exposures. Pulmonary rehabilitation has a significant impact of those who complete and a key non-pharmacological treatment.

Pharmacological treatments, initially excluding inhaled corticosteroids, will be described including a historic perspective, the mechanism of action of some of the key treatments e.g. bronchodilators. Key clinical papers will be described including their findings and any strengths and weaknesses.

Inhaled corticosteroids will be discussed in detail from early negative studies when used alone, through their licensing in dual combination inhalers through to triple combination inhalers. The role of combination inhalers is important as it may impact on adherence, a key outcome. The clinical indications for using an ICS will be highlighted as their indications and potentially overuse is central to the clinical outcomes of the study in stopping these treatments.

The study will be described in detail along with its primary and secondary aims with a focus on both its feasibility and clinical outcomes. This will include all aspects of its procedure from recruitment, the clinical follow up and outcome measures used. Results will be presented for the primary and secondary aim with statistical analysis where appropriate.

The results will be discussed and potential reasons for the results explored in the context of the study population and how they compare to other published evidence. The concept of Prudent Healthcare will be introduced as an important driver with the Welsh Health Service and how this study may fit in with its principles.

Finally, the study will conclude with a view on the potential of a larger study and where this work sits with current evolving guidelines, practice and priorities in a health service with limited resources.

CHAPTER 2: AN OVERVIEW OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

2.1 What is COPD?

COPD is a common, preventable and treatable long-term condition, predominantly of the lungs but usually also impacts on other systems in the body. It is an umbrella term that encompasses both chronic bronchitis and emphysema and usually manifests in symptoms of chronic cough, sputum production and breathlessness. COPD is a complex heterogenous disease and this heterogeneity manifests itself in the wide variety of respiratory symptoms, systemic consequences and comorbid conditions. The main symptoms are often representative of any dominant underlying pathophysiology. Emphysema can cause breathlessness in the absence of any significant cough and sputum, or chronic bronchitis can cause cough and sputum in the absence of significant emphysema but can also cause breathlessness due to plugging of small airways by excessive mucous. Often sufferers have a combination of both emphysema and chronic bronchitis but the hallmark is the presence of airflow obstruction (see Figure 1). Airflow obstruction is progressive and usually results in worsening symptoms and function. Airflow obstruction can be present in the small airways or present by destruction of the lung parenchyma resulting in emphysema.(5)

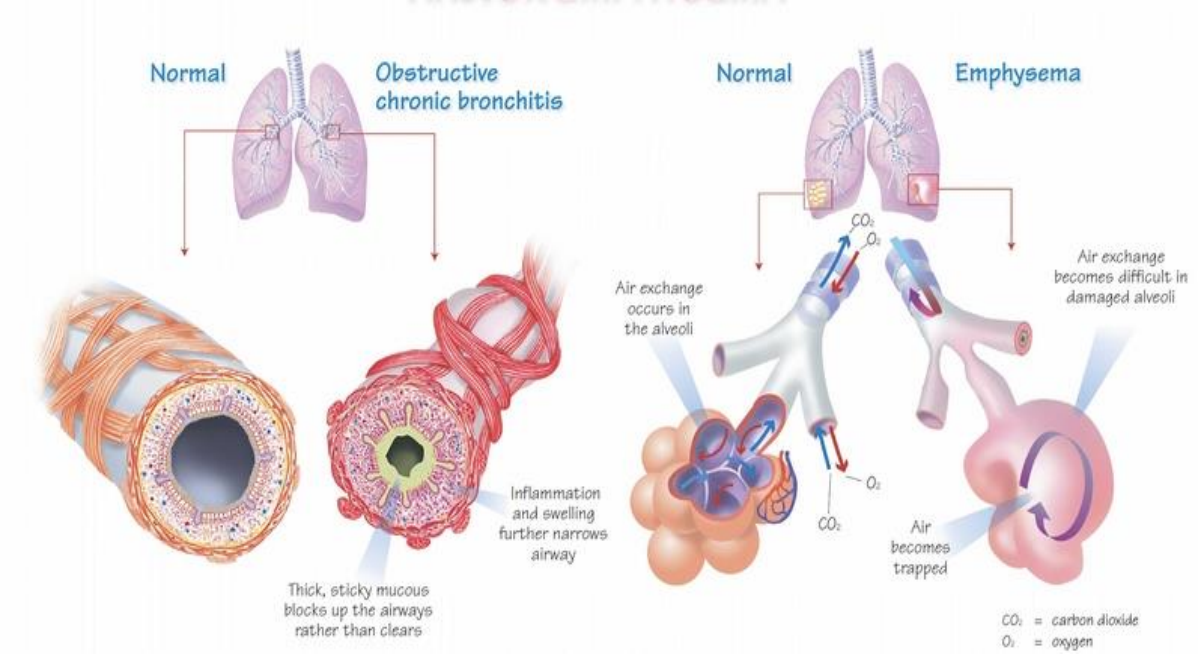


Figure 1: Illustration of chronic bronchitis and emphysema resulting in airflow obstruction, Taken from Living well with COPD(5)

2.2 Causes of COPD

COPD is caused by prolonged inhalation of noxious particles, most commonly tobacco smoke, lesser from occupational exposures or indoor biomass (cooking or heating) exposures where this typically is a problem in developing countries. Smoking is the main cause of COPD in 90% of cases in the United Kingdom (UK) (6) with an estimated only 15% of deaths now attributed to occupational causes of COPD. (7) The diagnosis of COPD from occupational causes remains underdiagnosed despite links going back to the 19th century and coming to the fore in the mid-20th century with reports linking it to coal dust and other trades exposing workers to dust. (8) Recent reviews have attributed an occupation population attributable fraction of 15% to COPD, highlighting the smaller but not insignificant contribution to the total burden. (9)

In The UK the Health and Safety Executive (HSE) has identified a list of substances if exposed to in high enough concentrations or over a period of time have the potential to cause COPD (10):

- Cadmium dust (PDF)
- Cadmium fumes
- Grain and flour dust
- Mineral dust
- Organic dusts
- Silica dust
- Welding fumes

Data published in 2019 by De Matteis analysed nearly 95,000 adults, aged between 40-69 years in a UK Biobank population-based cohort.(11) They all had accurate information relating to occupational history which was coded using standard occupational classifications, as well as smoking history, asthma history and lung function testing. The COPD diagnosis was defined by obstructive spirometry but no bronchodilators were administered prior to the test as is currently recommended (GOLD 2023).(12) They used a Poisson regression model with a robust error variance to estimate prevalence ratios. The final Model was adjusted for age, gender, recruitment centre and smoking history. Six occupations were statistically found to have a significantly increase in COPD risk: “sculptor, painter, engraver, art restorer”; “gardener, groundsman, park keeper”; “food, drink and tobacco processor”; “plastics processor, moulder”; “agriculture, and fishing occupations not elsewhere classified”; and

"warehouse stock handler, stacker". The authors concluded that in such a large sample, with good data and consistent results, that further investigation was warranted. They highlight the importance of occupation in COPD and that identifying high risk occupation would allow for implementation of focused preventative measures in reducing further morbidity and mortality.(11)

The inhalation of noxious particles in the susceptible host results in inflammatory changes in the lungs with increased numbers of inflammatory cells such as neutrophils, alveolar macrophages and T-lymphocytes. This inflammatory response is thought to play a significant role in the chronic damage resulting in airflow obstruction and alveolar damage characteristic of COPD.(13)

Host factors such as low birth weight and childhood lung injury through infection increase the risk of COPD.(12) Genetic factors appear to be important with familial links being significant (14) as well as mutations in the SEPRINA gene causing α-1-antitrypsin deficiency being a cause in a very small number of people and usually results in severe COPD especially if they smoke.(15) A recent UK biobank genetic study in over 400,00 people of European ancestry identified 279 genetic signals, 139 being new signals which strongly predict COPD in independent trans-ethnic cohorts. The individual effect size of these genes is small, but this work could lead to possible preventative and therapeutic treatments.(16)

Air pollution has a negative effect on lung function and increases the incidence and prevalence of COPD: Analysis was carried out on data gathered from the European Study of Cohorts for Air Pollution Effects (ESCAPE) against valid spirometric data from a UK biobank on 303,887 individuals between the ages of 40-69 years. Individuals living in areas with the greater inhalation of coarse respirable particles (between 2.5 μm – 10 μm) and nitrogen dioxide (NO_2), adjusted for sex, age, obesity, smoking status, asthma status and previous occupations linked to COPD- had lower lung function (FEV_1 −83.13 ml, 95% CI −92.50– −73.75 ml) and increased prevalence of COPD.(17) These results support an earlier cross sectional, observational UK study of 96,779 participants of which 5391 had COPD (prevalence 5.6%). They concluded that the higher exposure to ambient particulate matter by increments of 10 μg/m^3 resulted in higher odds of COPD (odds ratio 1·55, 95% CI 1·14–2·10) with urbanicity associated with higher odds and residential greenness being protective. Residential greenness was defined using a normalised vegetation difference index (NVDI), an index based on a reflective value from chlorophyll calculated from image pixels. (12, 18)

Living in a more ‘greener’ environment may be a marker of affluence, non-smoking status, healthy diet etc so the complex interactions between multiple genes and multiple environmental factors causing a heterogenous disease in itself – are all the subject of ongoing research. The current prevalent hypothesis is that COPD results from gene(G)-environment(E) interactions occurring over the lifetime(T) of an individual (GETomics) that can damage the lungs and/or alter their normal developmental /ageing processes.(12)

2.3 Prevalence of COPD

The British Lung Foundation (BLF) estimates there are approximately 1.2 million people in the UK diagnosed with COPD, 4.5% of adults aged over 40 years. Prevalence continues to increase either representing an increase in the disease or more diagnosis or both. (19) In 2019 Wales has a higher prevalence, 2.35%, compared to the UK average of 1.95%. (20) In newly diagnosed patients there is an association with standards of living with the highest numbers in the most deprived quintile in society and conversely the lowest prevalence of COPD in the least deprived quintile.(19) The heat map (Figure 2) demonstrates the significant variation in prevalence across parts of England but this data is not available for Wales.

There are significant numbers of people living with COPD in the UK who have not been diagnosed. In a high-risk group of 986 current or ex-smokers in the Lung Screen Update Trial (LSUT), 377 (38%) had spirometry testing consistent with undiagnosed COPD. If you exclude those with a known diagnosis of COPD (n=183), 47% of this select high risk group had no diagnosis of COPD but found to have spirometry consistent with COPD. 50% of those undiagnosed had moderate and 23% having severe or very severe airflow obstruction with 36% reporting symptoms of COPD.(21)

Data published in 2015 from a systematic review and meta-analysis estimates a Global prevalence of 11.7% (95% CI 8.4-15%), a 1% increase from the same work undertaken by the same group in 1990. (22)

Recent prevalence studies estimate that 11.8% of men, and 8.5% of women worldwide are affected by COPD. (23) In the UK around 1.8-2.5% of people are listed as having COPD on GP databases with smoking and age being the commonest risk factors. (24, 25) This is likely an underestimation of the UK

prevalence due to delays seeking help and inaccurate diagnoses. Moreover, smoking rates alone do not explain the geographical variation in COPD prevalence as it results from a complex interaction of environmental factors with passive smoking and air pollution (26), exposure to biomass fuels (27), early pre and post-natal lung development (28) and genetic susceptibility (29, 30) all contributing.

Around 74,000 to 80,000 people have been diagnosed of COPD in Wales – that's about the equivalent of a whole Millennium Stadium's worth of people. Around 3,000 people are diagnosed with COPD every year in Wales. (31)

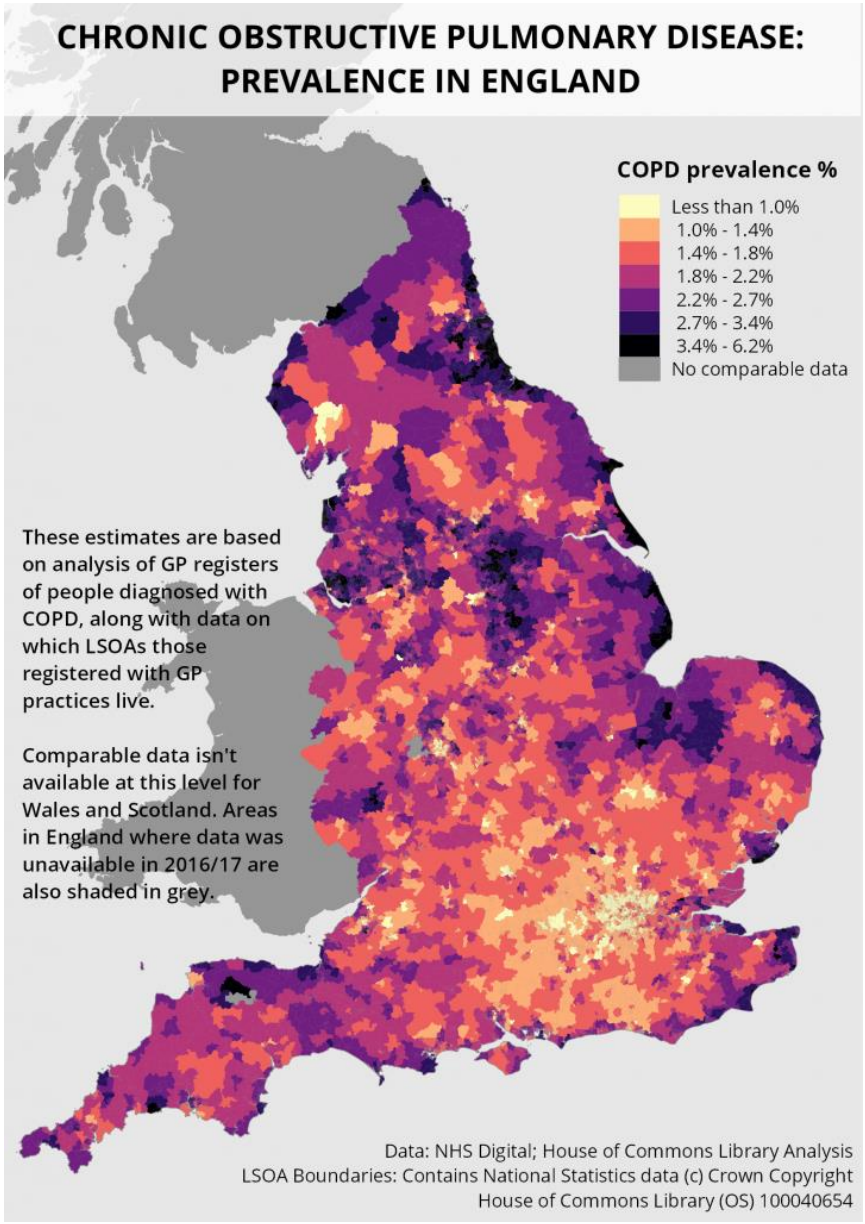


Figure 2: Variations in the prevalence of COPD across England. (32)

2.4 Diagnosing COPD

Diagnosis is made from a combination of symptoms, typically gradual breathlessness increasing slowly over time resulting in a reduced exercise capacity accompanied by symptoms of chronic cough, sputum production and possible recurrent respiratory tract infections. Symptoms show little day to day variation and tend to be predictable. These along with a history of significant prolonged exposure to noxious particles should lead to the undertaking of lung function testing in the form of spirometry. Not performing spirometry is the biggest predictor of an incorrect diagnosis of COPD. (33) Post bronchodilator spirometry should confirm the lack of significant reversibility and presence of airflow obstruction with a forced expiratory volume in 1 second (FEV_1) being <0.7 of the forced vital capacity (FVC).(34) Although guidelines refer to the cut off of <0.7 the issue with this being that with older individuals the distribution of results in a healthy population is not proportional to the mean which could result in a value of <0.7 falling within the lower level of normal (LLN) and not obstructive. Using the LLN of the lower fifth percentile increases the test sensitivity and will increase the detection of true disease. (35) The use of varying criteria and regional guidelines results in huge variations globally with both under and over diagnosis resulting in prevalence rates ranging from 3-21%. (33) To ensure reliable and valid test results spirometry testing should be performed in line with defined quality criteria as set out by The Association of Respiratory Technology and Physiology.(35)

There are a subgroup of individuals who can have symptoms +/- emphysema which can result in a normal FEV_1/FVC ratio (>0.7 or above the LLN). Symptoms may be to due to other physiological abnormalities such as hyperinflation, gas trapping and a reduced gas diffusion capacity. These have been described as Pre-COPD with a new term of Preserved Ratio Impaired Spirometry (PRISm) proposed.(12)

The figure below (Figure 3) represents obstructive spirometry in the flow volume graph on the left and volume time graph on the right with an FEV_1/FVC ratio of 0.38 (or 38%). (36)

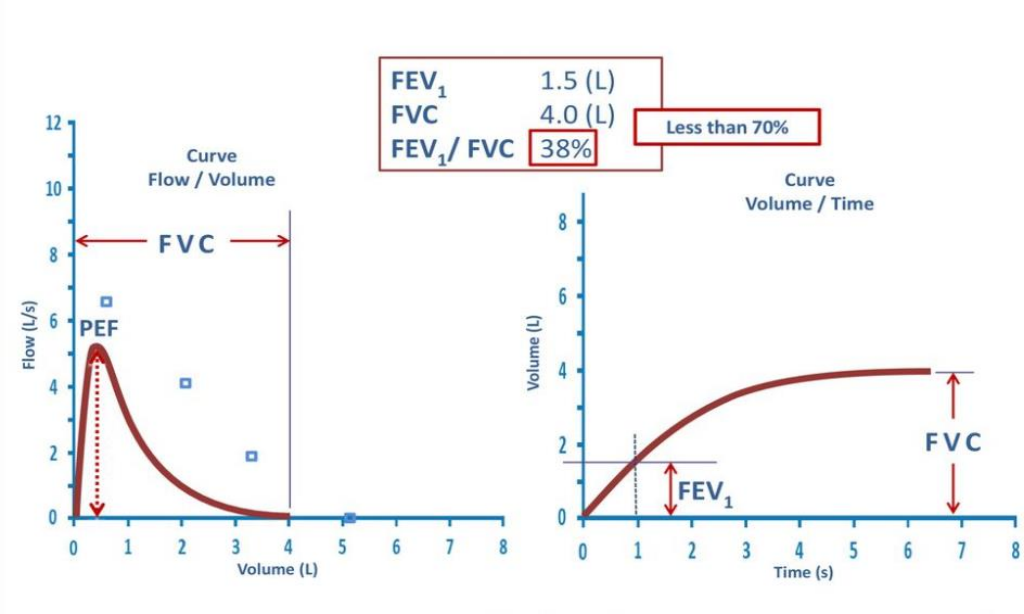


Fig 3: Obstructive spirometry(36)

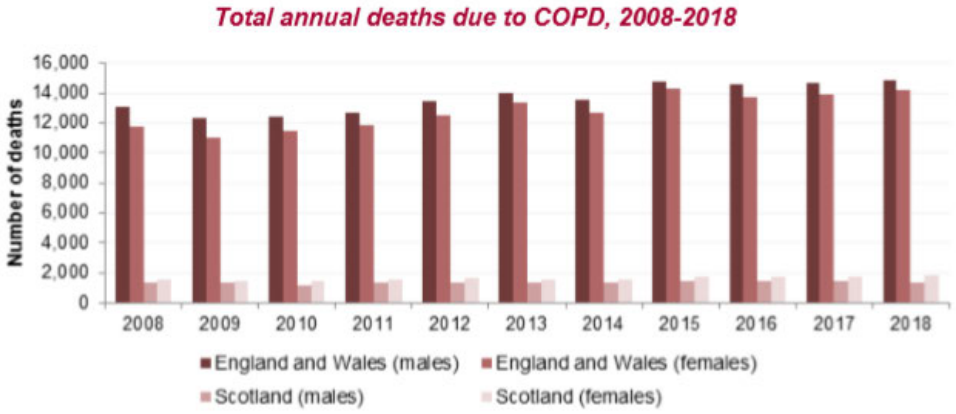
2.5 Exacerbations in COPD

Exacerbations are defined as a sustained worsening of symptoms (days) above the normal day-to-day variation in health status, needing a change in treatment. (12) Moderate exacerbations are those requiring parental steroids or antibiotics and severe exacerbations are those requiring admission to hospital for at least 24 hours. (37) Exacerbations cause a large economic burden; they are the third commonest cause of hospital admission in the UK; the average cost per COPD patient per year in the UK was £819 over 10 years ago with a significant amount of cost associated with exacerbation treatments. (38) US data showed that in 1 year, COPD caused 1.5 million emergency department attendances, 726, 000 hospital admissions and 119, 000 deaths. (39) Exacerbations are associated with higher mortality rates in COPD (40-42), more rapid decline in lung function (43) and worsening health status. (44, 45)

Despite better understanding of disease mechanisms, diagnosis and more treatment standardisation, COPD remains a major public health problem. It is a leading and growing cause of morbidity worldwide (37, 46, 47) and is now the third highest cause of mortality (23) 12 years before it was predicted to be. (22) There are no curative treatments for COPD except extremely rarely lung transplant and the contributory roles of co-morbidities and poor social circumstances are also increasingly recognised. (48, 49)

2.6 Mortality in COPD

COPD is currently the 3rd leading cause of death worldwide.(50) The latest data from the World Health Organisation suggests overall mortality from COPD reduced globally from 2019 to 2020. (51) Mortality continues to increase in the UK (See figure 4) with now over 30,000 deaths annually attributed to COPD. (7)



Figurer 4: Total annual deaths from COPD by year in UK 2008-2018(7)

2.7 Predictors of mortality

Spirometry can help stratify the severity of COPD as measured by the degree of airflow obstruction in relation to the FEV_1 compared to standardised reference range for someone of the same age, gender and height:

- mild ($\geq$ 80% predicted)
- moderate (50-79% predicted)
- severe (30-49%predicted) and
- very severe (<30%)

The severity of airflow obstruction as measured by spirometry does not always correlate strongly with symptoms as there are other causes of a patients' perception of breathlessness. However, there is a positive association between severity of airflow obstruction and degree of cough, breathlessness quality of life and exercise capacity.(52, 53) Moreover, Soriano et al identified FEV_1 is an important prognostic indicator in examining deaths from 1990 to 2015 across 195 countries in a systematic analysis for the Global Burden of Disease Study.(54)

Other validated measures of breathlessness and function for example, Medical Research Council (MRC) dyspnoea scale, Chronic Respiratory Questionnaire-Self Reported (CRQ-SR) and COPD Assessment Test (CAT) are also useful in assessing severity and prognosis.(55-57) Composite scores, for example. BODE (body mass index, obstruction, dyspnoea, exercise capability) are better predictors of prognosis than any single measure but are not always practical to use in clinical practice as require time and staff. (58)

Landbo et al retrospectively analysed data from the Copenhagen City Heart Study of over 3,000 participants with lung function defined COPD. They concluded that those with a low BMI (<20Kg/m^2) compared to normal BMI had a greater mortality risk (relative risk 1.64, 95% CI: 1.2-2.23) with the most risk in those with severe disease (relative risk 7.1, 95% CI: 2.97-17.05).(59)

Exacerbation frequency is a predictor of mortality. A group of 320 patients with COPD were followed over 5 years and exacerbation data recorded. Those with $\geq$ 3 or more exacerbations requiring hospital admission compared to those with none had a 4.3 greater mortality risk ($p<0.0001$, 95% CI 2.70 to 6.88).(60) Even exacerbations that do not require hospital treatment, i.e. moderate, are associated with an increased mortality risk. Two in any 12 month period has an increased mortality risk of 1.8 (95% CI 1.19–2.70). (61) Comorbid diseases

such as cardiovascular, diabetes, hypertension are more common in those with more severe COPD (defined by lung function) and also add to risk of hospitalisation and mortality in analysis from a cohort of over 20,000 participants from 2 large US databases. (62)

2.8 Morbidity and burden of COPD (cost to patients, cost to the NHS, cost to society)

The European Union (EU) has estimated that COPD accounts for 56% of the direct costs of treating all respiratory diseases – 38.6 billion euros a year.(63) With prevalence predicted to increase, costs for England alone were expected to reach £2.32 billion a year by 2020. (64) In the UK, COPD emergencies account for the second highest reason for hospital admission (130,000/year) with 30% of these patients being readmitted within 3 months. They also account for 1.4 million GP consultations. (65) Not only is it a disease of the lung but it results in systemic inflammation contributing to many other prevalent comorbidities such as cardiovascular disease, osteoporosis and depression.(66) Other systemic manifestations include muscle wasting and cachexia with low body mass index, resulting in an increased risk of mortality in COPD.(59)

Sufferers with COPD have to live with slowly worsening symptoms of breathlessness, often cough, fatigue which all limit their function and eventually independence if the disease becomes severe. They may experience respiratory infections, hospital admissions and a likely early death. It may be difficult to work causing financial worries, putting pressure on relationships and potential for social isolation. The psychological impact can be huge with high levels of anxiety and depression. COPD is ranked 8th in a global list of conditions causing disease burden as measured by disability-adjusted life years (DALYs).(67)

2.9 Treatment goals in COPD

The treatments for COPD aim to improve mortality, reduce the impact of both physical and psychological symptoms, improve function, reduce the risk of exacerbations which can accelerate decline in physical function and lung function and to overall slowdown disease progression. (12, 68)

These goals can be supported by both non-pharmacological and pharmacological interventions.

2.91 Adherence to inhaled medication in COPD

Adherence rates to inhalers in COPD appear to be consistently poor and can be measured in a number of ways. Issuing of prescriptions although only a marker of collecting a drug (and not necessarily taking it) seems to be favoured as it is easy to measure. Typically, an 80% collection rate is often described as good adherence. There have been 9 studies, all in populations of patients with COPD taking maintenance inhaled therapies. All are different in design and within different health care systems from around the world, but all used the 80% cut off as a marker between good and poor adherence. In these studies, poor adherence (<80% pick-up) was seen in 41-93% patients with a mean of 71.6% patients.(69-77)

Adherence to treatment is an important factor in improving clinical outcomes so it is important to identify and address poor adherence or non-adherence. Issues relating to non-adherence are complex and can be separated into 3 broad areas (78):

1. Medication issues
    a. Complex regimes
    b. Multiple inhalers
    c. Inhaler technique
    d. Efficacy/time to onset
    e. Cost
2. Unintentional
    a. Age related factors
    b. Forgetfulness
    c. Misunderstood directions
    d. Comorbidities
    e. Health literacy
3. Intentional
    a. Perception of treatment/illness
    b. Denial/anger about disease

c. Inappropriate expectations

d. Dissatisfaction with health professionals

e. Cultural/religious issues

A Cochrane review in 2021 could not determine with any certainty which interventions if any, had an impact on improving adherence in patients with COPD. They suggested that combining approaches may offer the best outcomes and that some had possibly had an impact on hospital admissions but not quality of life. More studies are required with better design and more detailed information. (79)

It is important to note that co-production or shared decision making may have a significant part to play in improving treatment adherence in a population where adherence rates are low.(78) A survey of 450 patients in a south London community regarding general medication and prescriptions for many different conditions had a response rate of 79%; 60% who'd had recent changes to their medication did not feel they'd been involved in the decision making but 62% had wanted to be. In a follow-up survey, 37.5% felt their medication counselling could have been improved and most patients (89%) would make use of a medicines use review (MUR) service. A sample (n=18 with a diagnosis of COPD) went on to have semi-structured interviews for qualitative analysis which produced 3 themes around their experiences:

1. A lack of patient centred care and shared decision making

2. Minimal medication counselling provided

3. Lack of awareness around MURs.(80)

Page`s-Puigdemont et al conducted a qualitative study relating to patients' perceptions of medication adherence with 36 patients (mean age 65yrs with a mean of 2.3 comorbidities each) with a range of illnesses, including respiratory and chronic conditions. They interviewed them in 5 small groups and undertook a thematic analysis from transcripts. They identified 3 themes that could potentially be modifiable:

1. Their health beliefs

2. Patient-prescriber relationships

3. Their motivation and perception of illness control.

They concluded that strategies to improve adherence should focus on the shared decision making and patient education. (81)

Chrystyn et al in 2014 reported a cross-sectional, real-world survey of doctors and their patients: they included hospital specialists (n=683), primary care physicians (n=760) and COPD patients (n=1143). The physicians provided clinical data and baseline characteristics but also had to rate how they perceived their patient's overall adherence on a 5-point Likert scale ranging from 'not all compliant' to 'fully compliant'. Patients themselves completed generic health related quality of life questionnaires and sleep questionnaires but also a 7-point Likert scale to indicate how satisfied they were with their COPD maintenance inhaler. There was a significant association between patient satisfaction with their inhaler and compliance (χ^2-df = 89.7; p < 0.001) and fewer maintenance drugs (χ^2-df =17.7; p<0.001). They found a small but statistically significant association between treatment compliance and a reduction in exacerbations (R^2 = 0.037; p=<0.001) and hospitalisations due to exacerbations (R^2 = 0.025; p < 0.001). There was a direct association between patient inhaler satisfaction and a reduction in exacerbations (R^2 = 0.03; p < 0.001). Inhaler satisfaction centred around size, durability and ergonomics. Although potentially important, the weakness of this study lies in its subjective measure of adherence open to individual physician and patient recall and reporting bias.(82)

Correct inhaler technique as well as confidence in your inhaler technique may have an impact on health-related quality of life. Amin at al reported the results of a study designed to explore the impact on both physician and patient reported confidence on inhaler technique, subsequent adherence and health-related quality of life. 373 patients who had COPD were recruited by 134 physicians with regular experience managing COPD. Physicians reported on patient demographics, comorbidities, medication, inhaler device training and confidence in their patient's inhaler technique on a 5-point Likert scale. Patients also reported their confidence on the same 5-point scale as well as generic and disease specific health related quality of life questionnaires. Patients completed the validated Morisky Medication Adherence Scale (MMAS-8), providing a measure of treatment adherence. Low patient confidence in inhaler technique was significantly associated with patients who had depression (p=0.009), anxiety (p=0.03) and heart failure (p=0.44). Low patient and low physician confidence in inhaler technique was significantly associated with low treatment adherence and high confidence was associated with high adherence. High confidence was also significantly associated with higher quality of life and these patients also had fewer

comorbidities, less depression (p=0.0034) and higher education levels. Identifying the correct inhaler for a patient and providing ongoing education and support to maintain confidence and technique may improve adherence and so clinical outcomes.(83) The importance of adherence has even led to be the proposal it being recognised as a ‘treatable trait’ that deserves specific attention and intervention.(84)

CHAPTER 3: NON-PHARMACOLOGICAL TREATMENTS

3.1 Smoking cessation

By far the biggest cause of COPD in the UK is smoking. An estimated 13% of adults still smoke, with 6% more in the most deprived compared to the least deprived areas of Wales. 45% try and quit in any year and 1 in 5 will develop COPD. (85)

This means that 4 out of 5 smokers do not develop COPD. Whether this is because they die of other conditions before developing COPD or have a genetic predisposition to protect against lung damage is still unknown.

In terms of primary prevention in the UK, reducing the prevalence of smoking will have the biggest impact on reducing the prevalence and impact COPD. If people do not start to smoke or only have minimal exposure to cigarette smoke, then they cannot develop smoking related COPD.

3.2 Secondary prevention

As smoking causes and continued smoking accelerates the decline in lung function, therefore smoking cessation has the greatest potential impact on the disease trajectory.(12, 68) The Lung Health Study concluded that in the year following cessation airflow obstruction may improve and continued cessation reduces the decline in FEV_1 by about 50% when compared to those who are unable to quit, saving about 47mls or 2%. (86) Figure 5 illustrates the average rate of decline in FEV_1 increased in smokers over time when compared to those who quit from a mean in the first year of 49mls up to a mean over 5 years of 62mls. (86) Subsequent longer term follow up of this cohort 11 years after entry into the original study found very similar findings to the original study in that those who quit and sustained their quit had the best preserved lung function with the slowest decline (21.5mls/yr), those who continued smoking had the most rapid decline (54.2mls/yr) and those who were intermittently smoking had a much faster decline than those who quit but was better than those who never quit (30.2mls/yr).(87)

Smoking cessation will also reduce the number of acute exacerbations and lung infections, another cause of accelerated decline in COPD.(88)

It may be more difficult for smokers with COPD to quit smoking when compared to those who do not have COPD. This is based on them having higher Fagerström test scores for nicotine dependence, inhaling more cigarette smoke as measured by exhaled carbon monoxide (eCO) levels and lower levels of self-efficacy or self-esteem that hamper their ability to quit. (88)

Combinations of both psychological or behavioural support and pharmacotherapy appear to be the most effective in improving sustained quit rates. (89)

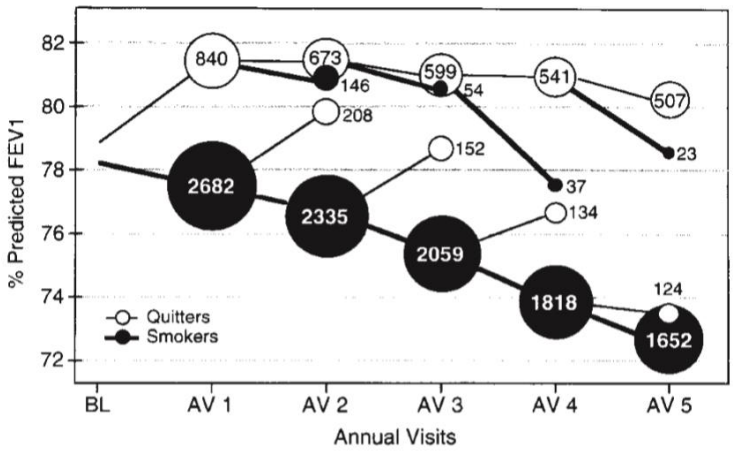


Figure 5: Decline in FEV1 in smokers compared to non-smokers with airflow obstruction(86)

3.3 Occupational exposures

Minimising exposure to occupational causes of COPD can be both a primary preventative measure or secondary measure to slow down disease progressions. Thus, identification of high risk professions and reducing workplace exposures is important in the fight against COPD. (11)

Employers have a legal responsibility under Control of Substances Hazardous to Health (COSHH) Regulations 2002 to control the exposure to any hazardous material in order to protect their employees' health.(10) These could include:

- Mechanical controls e.g., vacuums, personal protective equipment
- Administrative controls e.g., surveillance schemes, record keeping, education/training, supervision
- Operator controls e.g., following instructions

If employees are significantly exposed to substances known to cause COPD, then employers must put health monitoring in place.(90) Typically this would include:

- Assessing an employee's respiratory health before they start employment possibly using questionnaires and lung function
- Reporting to the occupational health department any suspicious respiratory symptoms
- If the employee smokes, support them stopping or cutting down
- Monitoring sickness

3.4 Pulmonary Rehabilitation

Combinations of exercise, education and stress management in the form of pulmonary rehabilitation has for some time been proven to be effective in significantly improving and sustaining physical activity and psychological well-being for patients with COPD.(91) In this seminal paper by Griffiths et al, 200 patients were randomised to 2 matched groups to receive an 18 session, 6 weeks of outpatient pulmonary rehabilitation or standard care at that time. They were followed up for 12 months. There was no difference in hospital admissions within the 12-months but bed days were significantly less in the rehabilitation group, 10.4 vs 21.7 days (p=0.022). The rehabilitation group did have more attendances to their primary care practice (presumably as they now knew their symptoms better) but they less home (emergency) visits than the control group. The rehabilitation group had both a significant and clinically important difference in quality of life as measured by 2 disease specific questionnaire, St George's Respiratory (SGRQ) and Chronic Respiratory Disease (CRQ) questionnaires at the end of the 6 weeks intervention and this improvement was maintained but smaller at 12 months. The control group had a steady decline in quality of life throughout the 12-month period. Further cost analysis of this study demonstrated it to be cost effective as measured by quality adjusted life years (QALYs) – perhaps even cost-saving with a 0.64 probability of cost per QALY being below £0.(92)

A Cochrane meta-analysis (93) since in 2015 of 65 randomised controlled trials of Pulmonary Rehabilitation in COPD found both statistically and clinically important differences in dyspnoea when measured by CRQ (>0.5) with a mean change of 0.79 (95% confidence interval (CI) 0.56 to 1.03 n=1283, 19 studies) or the SGRQ (improvement of 4 units) with a mean change -6.89 (95% CI -9.26 to -4.52; N = 1146; studies = 19). The quality of evidence was graded as moderate. Pulmonary rehabilitation improved exercise capacity as measured by a 6-minute walk test by a mean of 43.9m (95% CI 32.64 to 55.21; $Tau^2 = 713.49$; $I^2 = 74\%$; n=1879, 38 studies), exceeding the minimum clinically important difference of 30m. Analysis was not as favourable with the incremental shuttle walk test with only a mean change of 39.8m (95% CI 22.38 to 57.15; $Tau^2 = 181.56$; $I^2 = 32\%$; n=694, 8 studies) below the minimum clinical important difference of 47.5m. The authors concluded that pulmonary rehabilitation results in moderately large and clinically significant changes in dyspnoea, fatigue, emotional function and enhanced controlled over their COPD. A previous metanalysis reported significant heterogeneity in studies but no overall benefit on hospital

readmission or mortality. The authors acknowledge the limitation of the data and the need for more studies were required. (94)

Pulmonary rehabilitation is now recommended in all national and international guidelines as a core component in managing people with COPD who are limited in their daily activities.(12, 34, 68)

Programs often last for 6-12 weeks, including two-weekly supervised sessions of about 2 hours in length and participants encouraged to do at least one other unsupervised. Sessions are supervised by combinations of therapists, exercise technicians and nurses with a group of 8-12 participants. At least 30 minutes should be devoted to exercise and time for education, self-management and relaxation.(95)

Access to pulmonary rehabilitation is variable with multiple barriers inhibiting the completion by those with COPD ranging from issues around referral, attendance when referred from non-attendance for the initial assessment to completion.(96) Referral rates from Primary Care have been estimated to be as low as 16%.(97)

3.5 Non-invasive ventilation

A meta-analysis of 17 RCTs including 1264 participants on the outcomes of acute non-invasive ventilation (NIV) used to treat hospitalised patients with acute hypercapnic respiratory failure demonstrated a mortality risk reduction of 46% (risk ratio (RR) 0.54, 95% confidence interval (CI) 0.38 to 0.76; N = 12 studies), the risk of endobronchial intubation reduced by 65% (RR 0.36, 95% CI 0.28 to 0.46; N = 17 studies) and a reduction in the length of hospital stay by 3.4 days (95% CI -5.93 to -0.85; N = 10 studies). Evidence strength was defined as ‘moderate’ as some studies had a small risk of bias but the metanalysis concluded that further trials to prove efficacy are unwarranted.(98) Guidelines worldwide are in agreement and recommend the use of NIV to treat acute hypercapnic respiratory failure.(12, 68, 99, 100)

Home non-invasive ventilation (NIV) may improve hospital free survival in those patients who’ve recently had an acute hospital admission requiring acute NIV and have persistent hypercapnia when added to and compared to long-term oxygen therapy (LTOT) alone.(101) However, there are studies with conflicting outcomes in this area which may be a result of

study design and the lack of optimisation of pressure support to achieve a significant reduction in hypercapnia.(12, 68)

3.6 Surgical intervention

The history of surgery in COPD is littered with misguided interventions including costochondrectomy, phrenic nerve crush, pneumoperitoneum, pleural abrasion, lung denervation, and thoracoplasty.(102)

Other than lung transplantation, most surgical techniques now involve removal or deflation of emphysematous lung tissue. The hyperinflation caused by emphysema or a bullae results in an increase work of breathing, dyspnoea, due an increase in the residual volume of air in the lungs and impaired mechanics. This causes compression on the healthier lung tissue reducing its ability to ventilate effectively and also, compression of the small airways. Removal of the diseased tissue allows for improved ventilation, gaseous exchange and reduction in symptoms.(103)

Bullae are defined as airspaces in the lung greater than 1cm in diameter and can be surgically removed - bullectomy. (104) A bullectomy may be indicated if the bullae occupies more than a third of the hemithorax and the patient has significant dyspnoea that has not responded to other interventions, although there are no randomised trials looking at outcomes. (104) Post-operative complication rates are high (43%) including prolonged air leak, atrial fibrillation and pneumonia but most patients get an improvement in dyspnoea and pulmonary function tests. (105)

Emphysema, particularly when prominent in the lung apices, can also be surgically removed but only in patients meeting very strict criteria. (106) This is referred to as lung volume reduction surgery (LVRS) and is effective in reducing dyspnoea, improving quality of life, exercise capacity and lung function. (107) The NETT study was the largest randomised controlled trail and compared standard medical treatment to LVRS and enrolled 1218 participants. LVRS did not have any impact on long term mortality with an initial higher 90 day mortality compared to standard treatment (7.9% vs. 1.3%) but with no significant difference at 29 months (relative risk [RR] 1.01, $p = 0.9$). (107) The inclusion and exclusion criteria for both the study and subsequent referral now for consideration of the surgery is extensive. Some criteria include being a non-smoker, non-diffuse emphysema, fitness for

surgery and completed pulmonary rehabilitation and the absence of significant comorbidities (e.g. bronchiectasis, severe pulmonary hypertension, profound chest wall deformity/kyphosis and a lung mass or concerning nodule).

Where LVRS required thoracotomy with all the attendant risks, endobronchial valves offer an alternative which can be undertaken by bronchoscopy with similar benefits and potentially less complications. (108) These one-way valves (allow air out on expiration but not in) are inserted into the airway leading to the emphysematous affected area of the lung lobe provided pre-procedure testing has revealed that the area has little or no collateral ventilation. This results in deflation of the emphysematous area with improvements in dyspnoea, quality of life, exercise capacity and lung function. (109) These benefits are greater than compared to standard care with both statistically significant and clinically important changes maintained at 12months for FEV_1 (p=<0.001), 6-minute walk test (p=0.002) and SGRQ (p=0.004). (108) Post procedure (<45 days) serious adverse events (prolonged air leak, pneumonia, myocardial infarction and deep vein thrombosis) were around 40%, similar to LVRS with mortality potentially less than LVRS with a 5.5% rate at 141 days. (107, 108). Endobronchial valves are still only offered in specialist centres (e.g. Cardiff for all of South Wales) with specific referral criteria in place to support appropriate patient selection.

3.7 Lung Transplantation

Lung transplantation was first carried out by Dr James Hardy in Jackson, Mississippi in 1963. (110) COPD is the most common indication for lung transplantation worldwide with over a 1000 carried out worldwide every year. (111) In selected patients with very severe disease it is now widely accepted to improve quality of life and functional capacity but may not improve survival as it carries significant risks with a 12 month mortality estimated at 15%.(104, 112, 113) Median survival now being 6 years but better in those given a double lung compared to a single lung transplant. (113) Due to the extensive selection criteria (114) and limited donors the numbers of COPD patients receiving a lung transplant in the UK is small with only 182 transplants for all lung conditions including COPD in the year up to March 2019. (115) COVID-19 had a further significant impact on lung transplant services in the UK. A retrospective review of the UK Transplant Registry compared a 3 month period during the outbreak of COVID to the same period the year before and found a 48% reduction

in donors, a 77% reduction in the numbers of transplants performed with a significant increase in deaths of people on the transplant waiting list ($p=0.0118$).(116)

CHAPTER 4: PHARMACOLOGICAL TREATMENTS IN COPD (EXCLUDING ICS)

4.1 Bronchodilators in COPD

The two main classes of bronchodilators are $beta_2$-agonists and antimuscarinics. They come in a number of formulations and are usually either short-acting in nature and require taking more frequently or long-acting and taken less frequently. Longer acting formulations are now the usual treatment of choice as are superior and more convenient than shorter acting preparations.(117, 118) They act on the airway smooth muscle causing the airways to widen, improving measurements such as FEV_1 and FVC but also reducing dynamic hyperinflation, all of which can reduce breathlessness and increase exercise capacity.

4.11 Beta-agonist bronchodilators

Adrenaline, an alpha, beta 1 and beta 2-agonist, was first administered (successfully) subcutaneously for asthma in 1903 but had significant side effects due its actions on the other groups of receptors. Isoproterenol a more selective beta agonist, was developed around 1940 and the first published trials compared to placebo in asthma were published in 1949. Figure 6 is a photograph of an early vapouriser used to administer adrenaline. It was able to be administered by inhalation but again, because of its systemic effects and ability to stimulate all adrenoreceptors had significant side effects, particularly palpitations as well as coronary ischaemia when administered orally or subcutaneously. It was only through work by Ahlquist in 1948, that two adrenoreceptors were identified, alpha and beta, with different functions. Further work by Lands in 1967 discovered that there were two sub-types of beta receptors, $beta_1$ and beta $_2$, again with different functions (see figure 7). (119, 120) The $beta_2$ receptors (see figure 8) were found to be responsible for smooth muscle relaxation and hence bronchodilatation.

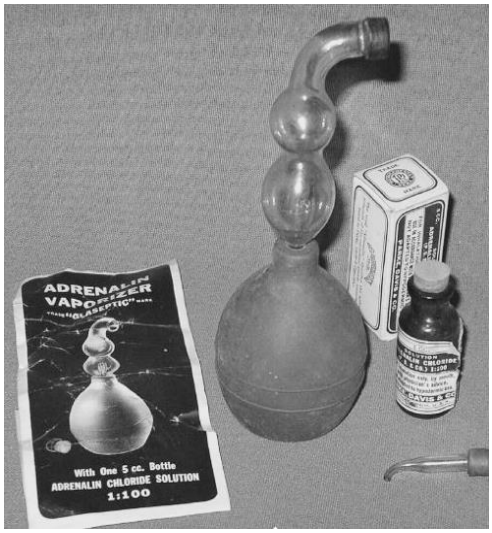


Fig 6: Vapouriser used in 1947 to administer inhaled adrenaline. (121)

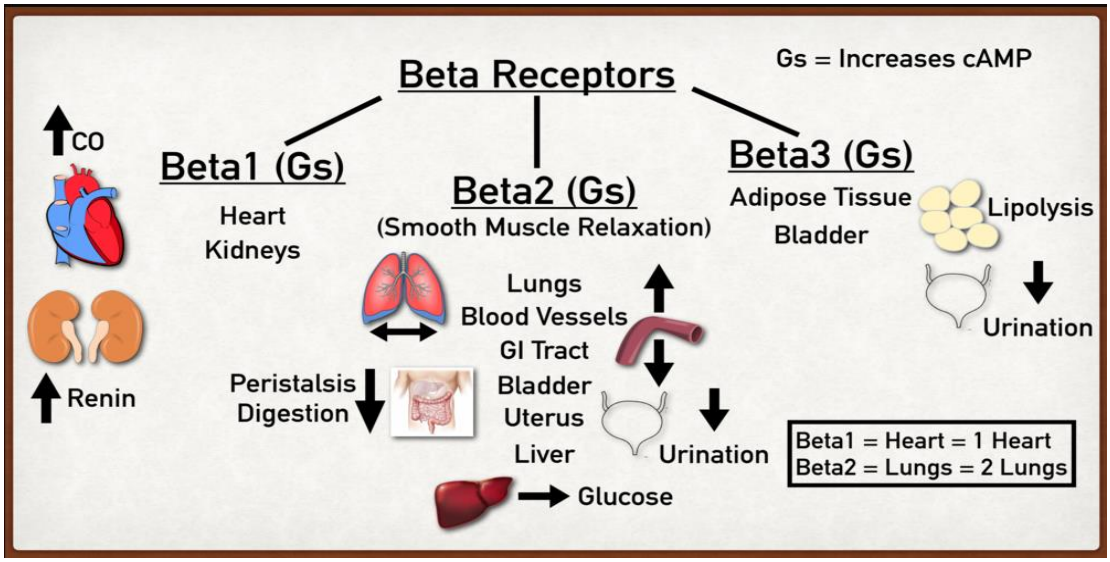


Figure 7: The distribution of beta receptors in the body. (120)

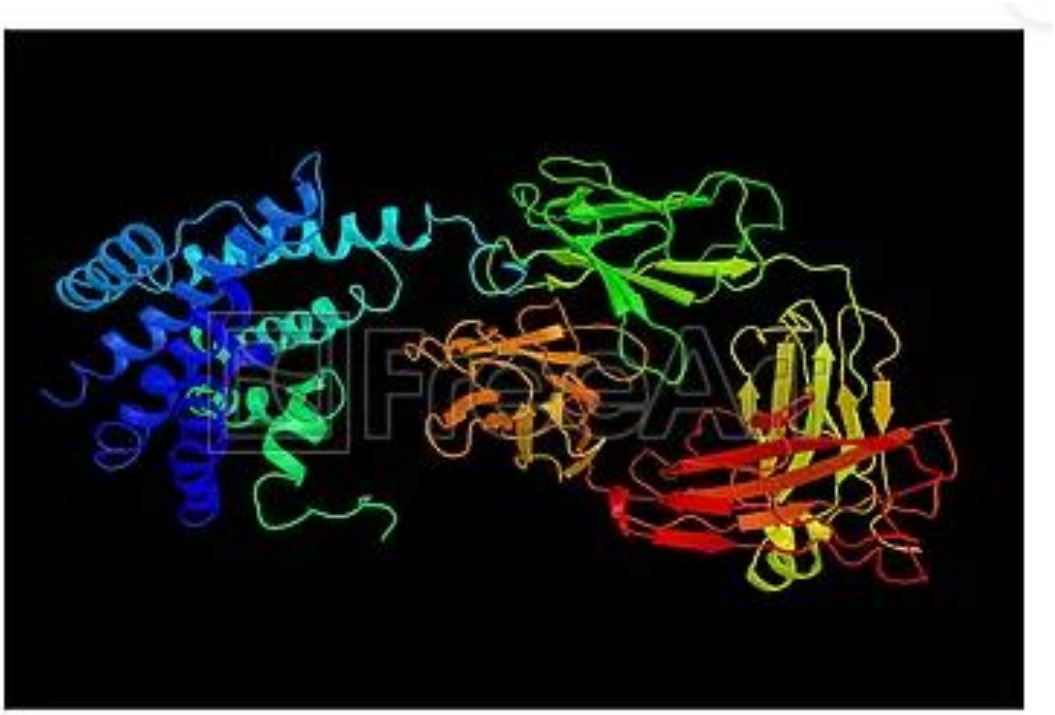


Figure 8: A beta$_2$-receptor antagonist. (122)

Work was already under way in the mid-1960s to develop and test drugs (salbutamol, terbutaline) that gave effective bronchodilatation with significantly less side effects, such as increased heart rate, as they primarily only stimulated the $beta_2$ receptors.(123) It was also discovered that side effects were reduced further if administered by inhalation compared to oral or subcutaneously. (124) We now know these as $beta_2$ adrenoreceptor selective drugs with Salbutamol being licensed for use in the UK in 1969. (124) In the early 1990s longer acting form of these drugs became available (salmeterol, formoterol) for asthma with effects lasting 12 hours.(119)

4.12 Cellular actions of beta-agonists

$Beta_2$ receptors sit on the airway smooth muscle cell wall and the presence of the beta-agonist activates adenylyl cyclase (AC) with the aid of a coupling protein (G_3). This leads to an increase in cyclic adenosine monophosphate (cAMP) which then activates protein kinase A (PKA). PKA causes relaxation of the airway smooth muscle by several mechanisms, removal of calcium ions from the cell and into intracellular stores, inhibiting the effect of myosin phosphorylation and opening of potassium channels to repolarise smooth muscle cells which may aid the movement of calcium ions into the intracellular stores (see figure 9).

Beta-agonists may have additional benefits in the airway. They can prevent the release of mast cell mediators which play a part in the inflammatory process, prevent microvascular leakage which can cause airway oedema, increase mucus secretion which may enhance mucociliary clearance and block the release of acetylcholine thereby improving the bronchodilator effect by reducing any cholinergic reflex bronchospasm. (125)

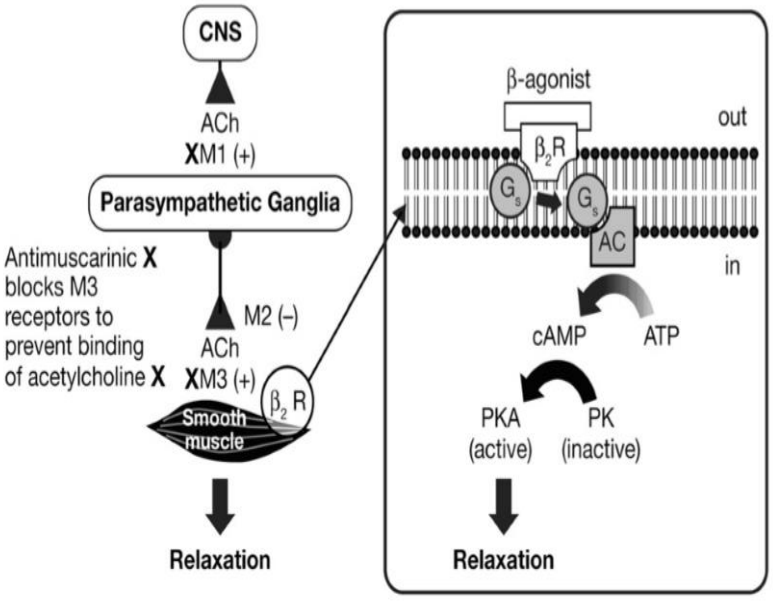


Figure: 9 Indirect and direct relaxation of smooth muscle. AC = adenylyl cyclase; β_2R = β_2 receptor; cAMP = cyclic adenosine monophosphate; G_s = stimulatory G protein; PK(A) = Protein kinase (A) (126)

4.13 Long acting $beta_2$ receptor agonist in COPD

Salmeterol, the first long acting $beta_2$ receptor agonist (LABA) was initially launched for use in asthma in 1990 and then COPD. In 1997 Jones and Bosh published the results of a 16-week placebo controlled double blinded study with 3 arms, placebo, Salmeterol 50µg twice daily and 100µg twice daily in 283 participants with symptomatic COPD.(127) Groups were well matched at baseline with a mean FEV1 1.3L (45% predicted). The main outcome measure was health related quality of life using SGRQ. The Salmeterol 50mcg group had a statistically and clinically important change in total SGRQ score of -5.3 (95% CI: -8.9, -1). The SGRQ in the higher dose of 100 µg did not change significantly. The general quality of life Medical Short form 36 questionnaire (SF-36) was also used with only a significant improvement shown in one of the 8 domains: Physical role functioning with a 12.4 point improvement (95% CI: 1.5,23.3). This study was a subgroup of a lager study with the same design of 674 participants. (128) Results showed a reduction in the daily symptom scores for both Salmeterol dose groups when compared to placebo (50µg, p=0.043; 100µg, p=0.01). Both active treatment groups demonstrated 7% increase in FEV_1 by the end of the study when compared to placebo but no significant difference between the 2 Salmeterol doses (p=0.404). There was no improvement between groups in 6-minute walk test results between groups (mean 401-422m) but the 50µg group were significantly less breathless than both the placebo (p=0.004) and 100µg groups (p=0.01). There were no significant differences in exacerbations between groups. Safety and adverse events were similar between groups other than the 100µg group reporting higher rates of tremor which was significantly higher than both other groups (p=0.005), being reported as pharmacologically predictable dose related.

In 2007 studies were beginning to be published using Indacaterol, an ultra-long once a day preparation that gives greater than 24hour efficacy with improvements in both lung function and the transition dyspnoea index (TDI) when compared to twice daily formoterol with a comparable safety profile in a groups of patients with moderate to severe COPD.(129) Several other preparations have become licenced for use in both COPD and asthma.(12, 68, 130)

4.2 Antimuscarinic bronchodilators

Antimuscarinic or muscarinic antagonists are also sometimes referred to as anti-cholinergic bronchodilators.

Atropine and its analogue from the deadly nightshade family, have been used for hundreds of years to relieve respiratory distress. In the 19th century it was a popular over the counter medication sold in the form of cigarettes or pipe tobacco but its use declined in the early part of the 20th century due to alternatives with less side effects. (131)

Early pre -licensing studies with Ipratropium in patients with chronic bronchitis, a short acting antimuscarinic, demonstrated a bronchodilator effect and hypothesised as to why these effects were different in asthma and COPD.(132)

4.21 Cellular action of antimuscarinic bronchodilators

Smooth muscle tone and mucus secretion in the lung is mediated by the autonomic nervous system via the cholinergic nerves. Branches of the 10th cranial (vagus) nerve terminate at the muscarinic cholinergic receptors (M receptors) on the parasympathetic ganglia within the thoracic cavity – acetylcholine being the primary neurotransmitter here. Increased vagal nerve activity plays a key part in bronchoconstriction and mucous gland secretion, thus blocking it results in a reduction in bronchoconstriction and mucus secretion. (see Figure 10)

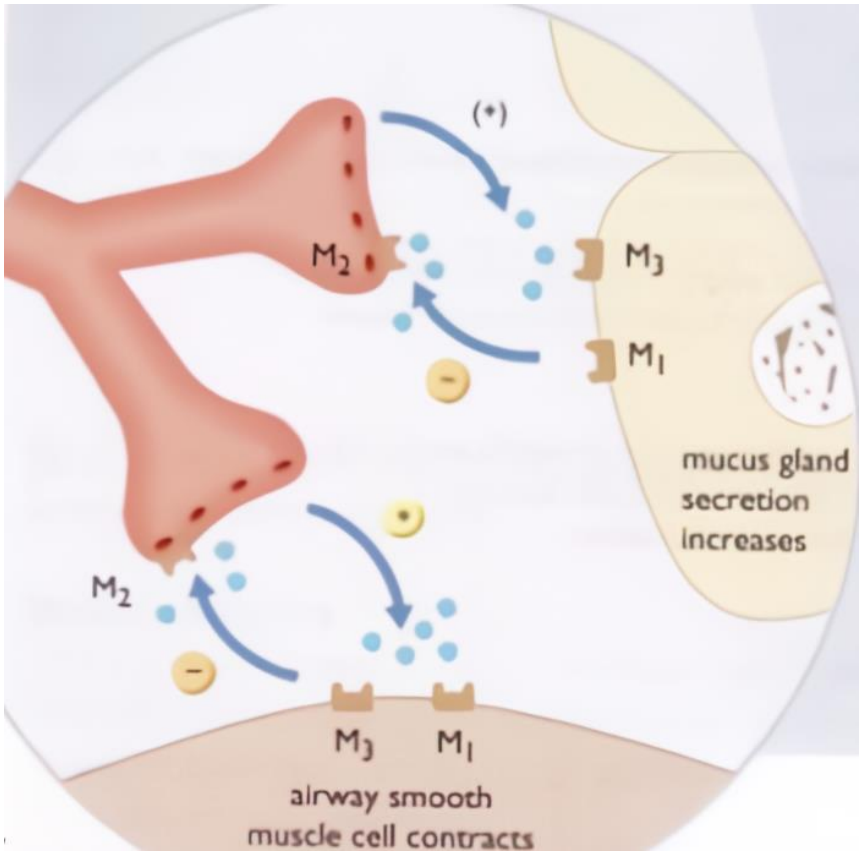


Figure 10: Bronchodilator acetylcholine receptor mechanism(133)

There are five M receptors, M_1 – M_5 with M_1 and M_3 being responsible for the mediation of bronchoconstriction and mucus secretion. M_2 inhibits the M_1 and M_3 receptors via a negative feedback mechanism so acts to inhibit bronchoconstriction. (134)

4.22 Antimuscarinic bronchodilators in COPD

Antimuscarinic drugs block the M_3 receptors on the airway smooth muscle to help prevent bronchoconstriction. Although they have all the benefits of beta$_2$-agonists they may be superior in reducing exacerbation rate when given alone compared to beta$_2$-agonists alone but again have no impact on long term decline in lung function or mortality. (135)

In 1973 an early pre-licensing double blind crossover study, 20 patients with chronic bronchitis were given inhaled Sch 1000 (Ipratropium) which was later launched as Atrovent™. It demonstrated a statistically superior and 4-hour sustained bronchodilatory effect when compared to placebo ($p=<0.01$) and salbutamol ($p=<0.05$) as measured by peak expiratory flow. It also produced the greatest positive change in airways conductance as measured by SGaw, a measure of airways resistance using body plethysmography, with the greatest against placebo ($p=<0.001$) and lesser but still significant superiority against salbutamol ($p=<0.05$). No significant side effects were noted and the authors concluded this new drug could have greater and more sustained bronchodilatory effects than salbutamol. (136) Ipratropium went on to be licensed for medical use in 1974 and a worldwide best seller that is still in use in nebulisers and inhalers today.(137)

Tiotropium was the first of a new line of longer-acting antimuscarinics launched by Boehringer Ingelheim as Spiriva in 2004 as the dry powder Handihaler™ device. It's ability to bind for longer to both the M_1 and M_3 receptors results in its longer duration of effect and requirement only to be taken once daily. It also has the beneficial effects of dissociating from the autoinhibitory M_2 receptor unlike the older shorter acting non-selective preparations of Ipratropium and Oxitropium. (131) A Cochrane review comparing Tiotropium to Ipratropium concluded these benefits translate into significantly improved lung function as measured by FEV_1 (mean difference 109 mL; 95% CI 81-137), a reduction in hospital admissions, reduction in exacerbations and improved quality of life but no impact on mortality in patients with COPD. (135) Alternatives to Tiotropium would not be available until 2012 when inhaled preparations of the long-acting antimuscarinics Aclidinium and Glycopyrronium became available for the treatment of COPD.

One randomised, double blind, double dummy controlled, 6-week, phase III study compared Tiotropium to Aclidinium and placebo in 414 patients with moderate to severe COPD. The study's primary endpoint was FEV_1 with both long-acting antimuscarinics demonstrated

significant improvements over placebo but not one superior to the other.(138) Symptom scores were significantly improved in both treatment groups from baseline but the Aclidinium group had greater improvements in all domains over Tiotropium but also reached statistical significance in relation to cough and sputum ($p<0.05$) which Tiotropium did not. The safety profile was similar for both drugs. When asked which device they preferred, the Tiotropium Handihaler™ or Aclidinium Genuair™, the patients' preference was for the Genuair™ with 80% vs 11% split ($p<0.0001$). This study was funded by the drug manufacturer.

A systematic review and meta-analysis comparing the efficacy of Tiotropium, Glycoperonium and Aclidinium for the maintenance treatment of COPD was undertaken and published in 2013. 21 studies were included, and the authors concluded that Aclidinium produced similar improvements to both Tiotropium and Glycoperronium for lung function, health related quality of life and dyspnoea. (139)

As well as the lung function improvements antimuscarinic drugs can also improve health status, reduce exacerbations and hospitalisations. There is no evidence they impact on long term decline in lung function or impact on all-cause mortality. (135, 140)

4.23 Dual verses single bronchodilators

Early small studies were unable to show any additional benefit of adding the two short acting agents (salbutamol and ipratropium) over each one individually presumably due to lack of statistical power. Later, larger studies were able to demonstrate significant improvements in lung function but no improvements in symptom scores by combining the drugs. (141, 142) There is some evidence that some people respond preferentially to anticholinergic/antimuscarinic than beta adrenergic agents and vice versa. This likely due to Arg-allele genetic polymorphisms in the ADRB2 gene (see figure 11). (143)

In this study, 111 patients were classified whether they responded better to salbutamol or oxitropium and the Arg allele was significantly more common in the oxitropium responder group. (143) The genetic basis of different responses to different classes of bronchodilators opens up fascinating possibilities to personalised prescribing based on genetic testing – akin to different responses to chemotherapy according to the Human Leukocyte Antigen (HLA) status and tumour expression of certain (onco) genes in e.g. breast cancer or lung cancer.

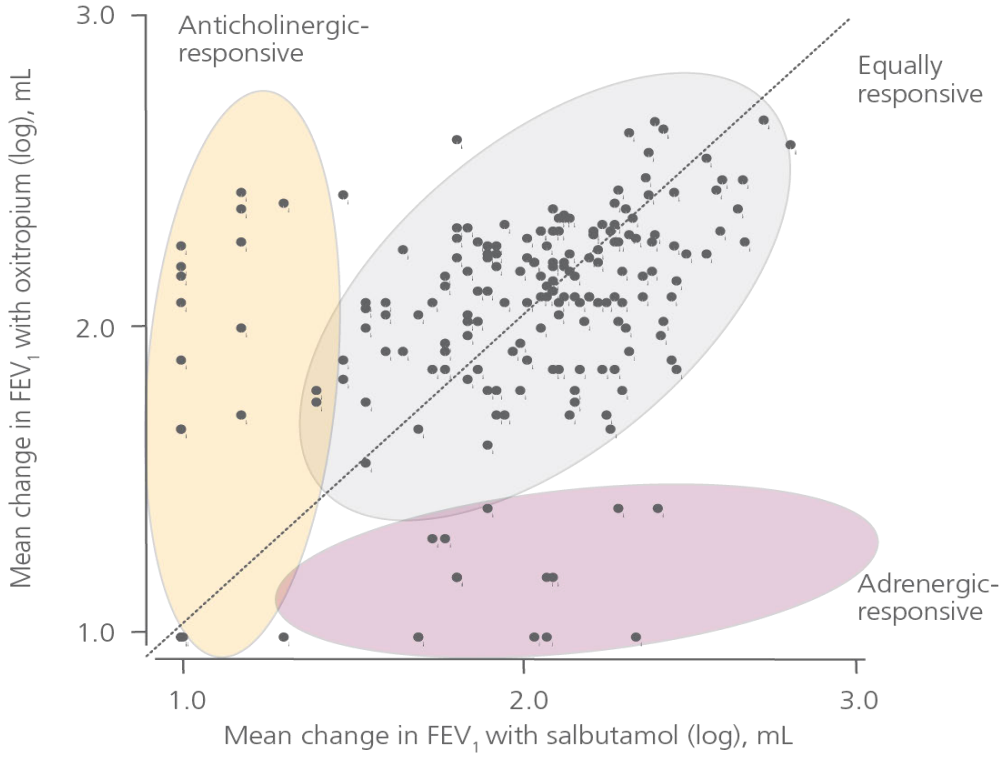


Figure 11**:** bronchodilator response to beta$_2$-agonists and antimuscarinics in patients with COPD.(143)

Another possible explanation of differential responses to bronchodilators is differences in the distribution and density of the different receptors in the lungs in different people.(144) This complimentary distribution patterns of muscarinic and beta$_2$-agonists at least in airways of dogs (see figure 12) suggest that targeting both pathways may provide better bronchodilatory coverage at the airway level overall than using either agent alone.(145)

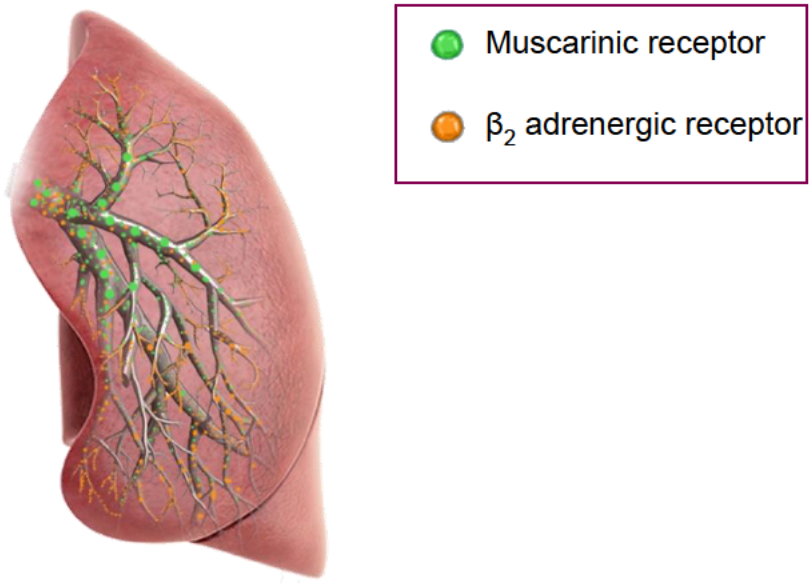


Figure 12: Distribution of muscarinic and beta2 receptors in the lung
Adapted from Gardenhire, 2015 (146) and Pelaia *et al*. 2014. (147)

Inhaling both classes of bronchodilator together has now been shown to have greater benefits in symptoms scores and (sustained) lung function over each alone and now the longer acting combined bronchodilators is accepted as the starting treatment for breathless patients with COPD.(34) A Cochrane meta-analysis of 99 high quality studies concluded that a dual combination inhaler containing both a long acting beta agonist (LABA) and a long acting muscarinic antagonist (LAMA) were superior to either each single component or combinations of an inhaled corticosteroid (ICS) and LABA in reducing moderate to severe exacerbations in a high risk population. (148) This is reflected in the 2023 GOLD Consensus statement.(12)

4.3 Long-term domiciliary oxygen therapy (LTOT) and COPD

For those clinically stable COPD patients prescribed optimal pharmacotherapy (at that time) who had chronic severe hypoxaemia (PaO_2 <8 kPa), using oxygen for greater than 15 hours per day has been shown to prolong life.(149, 150)

This statement is based on two landmark studies undertaken in the late 1970s and both aimed to achieve a partial pressure of arterial oxygen (PaO_2) > 8 kPa.

The multicentre US Nocturnal Oxygen Therapy Trial Group (NOTT) randomised 203 patients with hypoxemic COPD in an open label study to either 12 hours of oxygen overnight or continuous oxygen for 24 hours a day. (151) Hypoxemia was proven by blood gas and airflow obstruction by spirometry with other chest treatments given as clinically appropriate. Patients were excluded if they had had oxygen for 30 days in preceding 2 months or other comorbid conditions that may influence mortality, morbidity, adherence or ability to give informed consent. Oxygen was titrated to maintain a partial pressure of oxygen (PaO_2) between 60-80 mmHg. They were instructed on its use, followed up for at least 12 months (mean 19.3 months) if alive with weekly visits at home by a nurse for the first 6 months, then monthly after this. Adherence was measured subjectively by patient diaries and objectively by a timer.

Both groups were matched at baseline with a mean age approximately 65yrs, 80% males, matched cardiac comorbidities with a mean FEV_1 of 30% predicted and mean PaO_2 of 51mmHg. Smoking status, prior hospitalisations and weight or weight loss were not reported. The timers indicated that the nocturnal therapy group averaged 12hr/day (SD 2.5) and the

continuous therapy group 17.7hr/day (SD 4.8). They reported that as the continuous group used portable oxygen their use was under-reported as the timer could not account for this. The 12-month mortality was 11.9% (SE 3.2%) in the continuous group and 20.6% (SE 4%) in the nocturnal group with a 24-month mortality of 22.4% (SE 4.6%) in the continuous group and 40.8% (SE 5.5%) in the nocturnal group. This represented a significant difference in survival for the continuous therapy group (p=0.01) with an increased risk of death of 1.94 (95% CI 1-17-3.24) in the nocturnal group. The results were not adjusted for adherence but adherence was reported as very good so although unlikely to have impacted the results, nevertheless a weakness in the outcomes. There was no statistical difference reported in hospitalisations between groups.

The exclusion of 31% of the screened population due to significant other comorbid conditions does make this a selective group and not typical of the general COPD population. As both participants and researchers were unblinded to the intervention it does raise the possibility of bias, even unintentional. Failure to measure important cofounders that could impact on mortality such as prior hospitalisations, body mass index or fat free mass could have been important if not matched in both groups. Lastly, even with timers it may not reflect the time oxygen was inspired by the patient but merely the time it was switched on.

The Medical Research Council (MRC) Working Party published a UK multicentre randomised controlled trial in 1981 comparing oxygen used for 15hrs/day to no oxygen in 87 patients with spirometrically confirmed COPD, chronic hypercapnic respiratory failure ($PaO_2 \geq 40 \leq 60$mmHg) and clinical evidence of heart failure. (152) They were excluded if they had significant other lung disease, coronary artery disease or any other life-threatening disease. Oxygen was delivered either by cylinders, concentrators or liquid canasters. Participants were followed up every 2 months in hospital as well as home visits 'from time to time' and admitted to hospital early in any exacerbation. Measures of adherence were attempted by weighing cylinders, recording concentrator 'on time' and reviewing liquid oxygen use. They were followed up for 5 years with mortality being the primary outcome.

76% of the group were males and results were stratified by gender into treatment and controls but it is unclear if randomisation was undertaken by gender at enrolment or later for the results. The authors describe the groups as well matched other than the females' mean weight was less than the males (52.2 vs 68.1Kgs). Their mean ages were between 56-59yrs, FEV_1 ranged from 0.58 to 0.76Lt (% predicted FEV_1 was not reported). Their mean PaO_2 on air

was between 49-52mmHg, $PaCO_2$ 53-55mmHg, mean pulmonary artery pressure (PAP) 32-35mmHg and PaO_2 on oxygen corrected to 71-75mmHg with no difference in $PaCO_2$ between treatments groups (59-60mmHg). 6 of the males, 3 treatment and 3 controlled had pitting ankle oedema or a raised jugular venous pressure (JVP) with none reported in the females. No statistical analysis was reported in relation to the groups being matched or unmatched.

The all-cause mortality over the study period was 45% (n=19) in the treatment group and 67% (n=30) in the control group but with no difference between groups in the first 500 days. In both groups mortality rates were initially low then accelerated with a significant difference in rates after 500 days (12%/annum in treatment vs 29%/annum in the controls, p=0.04).

Mortality was significantly different in the female group with greater mortality in the controls compared to the treatment (log rank test, $p<0.05$). There was no significant difference in days spent in hospital between the 2 groups. For those who survived over 500 days there was little change in PAP, PaO_2 and $PaCO_2$ in the treatment group but worsened in the control group. Arterial stiffness increased slightly in the treatment group but increased more in the control group.

The use of oxygen therapy for 15 hours/day did appear to offer a survival benefit in this study. The mechanism may have been protective in slowing down the decline in PAP in a group in which it was mildly elevated. There remains the assumption that participants actually used their oxygen for the prescribed period and being an open label study, a degree of bias cannot be excluded. It is unclear who funded the study.

Figure 13 illustrates the survival curves of the 2 studies above with 24-hour use being superior to 12 hours and 15 hours being superior to no use. These results have led to the clinical recommendation that a minimum use of 15hours/day to gain survival benefits but additional use is encouraged if it does not restrict the individual and have a negative impact on their quality of life. (150) However, care should be taken when combining results from 2 separate studies where participants had some similarities (COPD, chronic respiratory failure) but some clear differences (heart failure, raised PAP and hypercapnia). Could these benefits be replicated in a general COPD population with chronic respiratory failure often with significant comorbid conditions excluded from these studies? Would new interventions such as long-acting bronchodilators, combination inhalers, acute and long term non-invasive ventilation and pulmonary rehabilitation impact on the supposed benefits? Home oxygen

prescription has no survival benefits in patients with mild hypoxaemia at rest or who have hypoxaemia during exercise.(153)

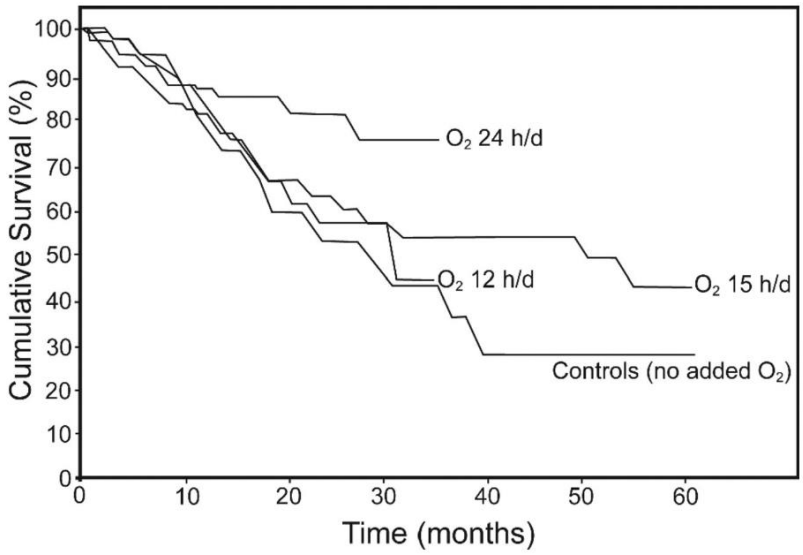


Figure 13: Overlapping survival curves for NOTT, 12 hrs oxygen verses 24 hrs/day (151) and MRC, no oxygen verses 15hrs/day (152)

4.4 Phosphodiesterase-4 (PDE4) inhibitors in COPD

PDE4 inhibitors block the metabolism of cAMP by intracellular enzymes causing an increase in cAMP concentration within the cell. This results in a rise in protein kinase A (PKA) which stimulates increased protein phosphorylation which inhibits pro inflammatory cells, inflammatory mediators and inhibition of fibrosis. (154) It is thought the main effect of PDE4 inhibition is due to its anti-inflammatory properties. The benefits appear to be strongest in the chronic bronchitic patients on optimal inhaled therapy who continue to have moderate or severe exacerbations. Rofumilast reduces the number of annual exacerbations when compared to placebo with pooled data from 2 large randomised controlled studies showing a 17% decrease (rate ratio 0.83, 95% CI 0.75-0.92) and improved pre and post bronchodilator FEV_1 by 48mls and 55mls respectively ($p<0.0001$).(154) It is an oral preparation and side effects are common, particularly gastrointestinal symptoms with 9% suffering weight loss (mean loss of 2.5 Kg). It has not been shown to impact on mortality. (155)

A systematic review and meta-analysis in 2020 which included 42 studies with 24,587 patients with moderate to very severe COPD, concluded that they provide a small benefit in terms of lung function and reduction in exacerbations but little impact on quality of life or symptoms. Side effects were common with up to 10% of patient having diarrhoea, nausea or vomiting with 7% experiencing a psychiatric event with a two to three fold increase in the risk of mood or sleep disturbance, although the overall number reported still being low.(156)

4.5 Prophylactic macrolides

Macrolides not only have antibacterial properties but also anti-inflammatory properties. The anti-inflammatory properties are seen at lower than usual therapeutic doses given for bacterial infection. (157) In a large randomised controlled study (158), 1142 participants had spirometry confirmed COPD (mean FEV_1 39/40% predicted in each group) and had to have had an exacerbation in the previous year (but were 4 weeks exacerbation free) or if exacerbation free on continuous oxygen in the form of long-term oxygen therapy. They received Azithromycin 250mgs daily or placebo for 1 year. The treatment arm had a significantly longer time to first exacerbation, 266 compared to 174 days ($p < 0.001$) as well as a significantly less total number of exacerbations per patient per year, 1.48 compared to 1.83 ($p = 0.01$). Figure 14 demonstrates the treatment arm had significantly higher number who were exacerbation free at 1 year ($p<0.001$). Although there were no differences reported

in the totals of any level of adverse event there was a greater (audiogram confirmed) decrement in hearing in the azithromycin group, 27% compared to 21% ($p = 0.04$) over the year. Although both groups were well matched, one of weaknesses of this study would be transferring its value to a specific patient population with such a heterogenous study population including 12-13% not having had an exacerbation in the preceding year, 8-10% not on any COPD medications and various numbers on single, double or triple inhaled compounds of ICS, LABA and LAMA.

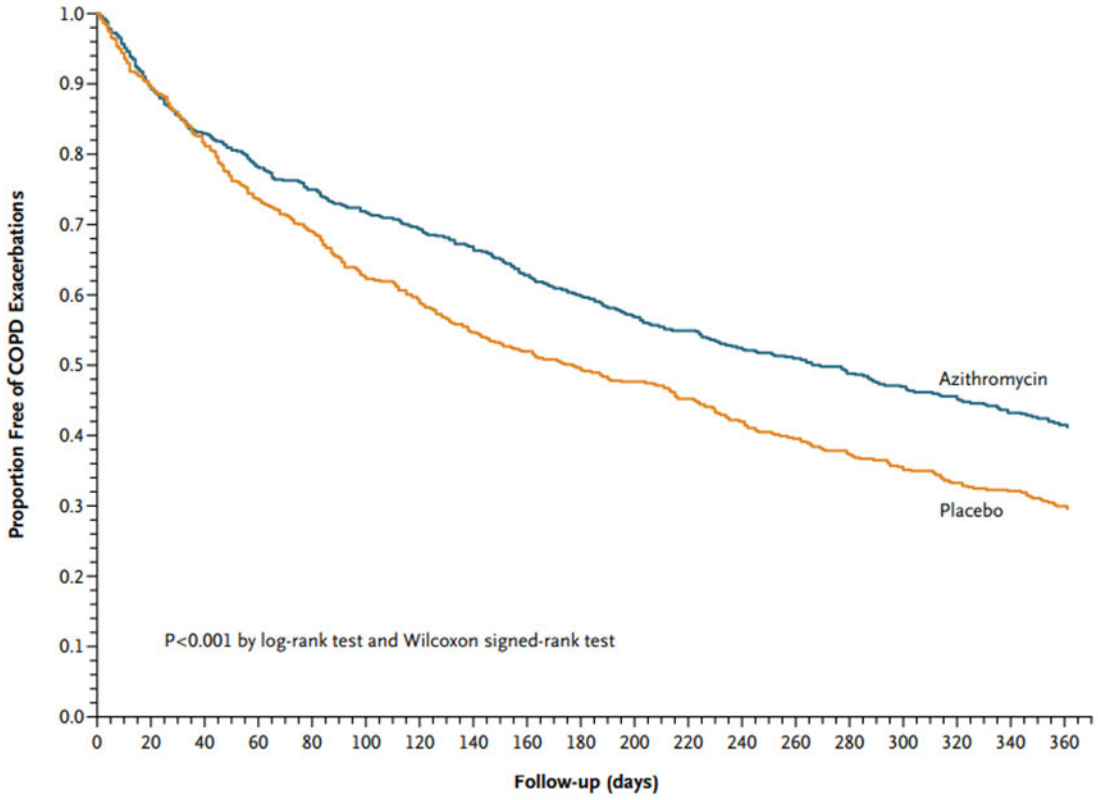


Figure 14: Proportion of participants free from acute exacerbations of COPD for 1 year.(158)

Other smaller studies have also demonstrated reductions in exacerbation rates using erythromycin (159) but more diarrhoea , 19% versus 2% (p=0.015).(160) In a post hoc analysis of the Albert study (158) there was a significant interaction between azithromycin and current smokers (p = 0.03) i.e. there was no reduction in exacerbation rates in current smokers (hazard ratio, 0.99; 95% confidence interval,0.71–1.38; P = 0.95). (161)

Little is known about long term macrolide safety as studies have only been followed-up over a year. The long-term effects on hearing and cardiac conduction are particularly unknown. Moreover, with the increasing awareness of antibiotic stewardship, concerns have been raised that routine nasopharyngeal swabs demonstrated a significantly higher level of macrolide resistance to colonising pathogens in those taking azithromycin compared to placebo 81% versus 41% (p <0.001). (158) There was a call in 2021 from the HTA and NIHR to look at appropriateness of long-term antibiotics in COPD and how to identify non-responders or how withdraw them.

4.6 Vaccinations

4.61 Annual influenza vaccination and COPD

A large US cohort study of 25,000 people (general population) aged >64 years over 3 years demonstrated significant benefits from the influenza vaccine when compared to an unvaccinated group.(162) Vaccination rates ranged from 45 – 58% with some evidence of increased benefits year on year if they received the vaccine. Compared to those who did not receive the vaccine, there was a 9% reduction for hospitalisations secondary to pneumonia or influenza (p<0.002) and a 12% reduction in admissions for all acute and chronic respiratory conditions (p<0.01). All-cause mortality was reduced by 15% over the 3 flu seasons in the vaccinated group (p<0.001). Vaccinations produced direct financial savings. Only approximately 10% of the 25,000 people had a chronic lung condition so the results may not be directly transferable to a population of COPD patients.

A Cochrane systematic review and meta-analysis looked specifically at the evidence for influenza vaccination in COPD.(163) They could only find 6 randomised controlled trials totalling 2,469 participants with COPD and a further 5 studies with an additional 4,281 participants who were elderly or high risk and some had a chronic lung condition. The total

number of exacerbations per vaccinated participant was reduced when compared to placebo (mean difference (MD) –0.37, 95% confidence interval (CI) –0.64 to –0.11; p = 0.006) but the quality of the evidence was low. Participants with COPD or those older participants experienced more local adverse reactions, but these were mild and transient. The authors also noted the size of the effect of vaccination was similar to large observational studies. Although the mortality effect favoured vaccination, they could not demonstrate any benefit with the limited number and small size of the studies for all-cause mortality (OR 0.87, 95%CI 0.28,2.7) or respiratory causes of death (OR 0.33, 95% CI 0.03,3.24).

4.62 Pneumococcal vaccination and COPD

A European review by Welte et al concluded community acquired pneumonia (CAP) carries a significant mortality and economic burden despite significant variation in rates and costs, with worse prognosis in patients with pneumococcal pneumonia. Mortality rates ranged from 1% to as high as 48%. Pneumonia incidence is higher in the older population (>65yrs) and in men with more antibiotic resistance also reported in these groups. Resistance was not associated with higher mortality but impacted on hospital admissions and lengths of stay. (164)

Bonten et al undertook a large 4-year randomised controlled, double blinded, placebo-controlled study of 84,496 adults over 65 years old. They used the 13-valent pneumococcal polysaccharide conjugate vaccine (PCV) which was efficacious in children but it's efficacy was unknown in adults.(165) A previous study in patients with COPD had concluded that 23-valent pneumococcal polysaccharide vaccine (PPV) was not effective in preventing CAP in those aged >65years.(166) With higher CAP rates in the elderly and COPD patients tending to be older, the efficacy in this high risk group is an important outcome. Bonten did not report the prevalence of any chronic conditions within the study population so the results are not directly transferable to a COPD population but the study does provide information on vaccine efficacy in this older age group. To support a diagnosis of CAP or other respiratory infections, patients received a chest X-ray and their urine was tested for serotype-specific antigen detection if they developed any symptoms. There was no difference in vaccine efficacy or placebo for all episodes of CAP but the vaccine had a protective effect against vaccine-type strains causing CAP (vaccine efficacy, 45.6%; 95% CI, 21.8 to 62.5), non-bacterial and non-invasive CAP (vaccine efficacy, 45.0%; 95% CI, 14.2 to 65.3), and other invasive pneumococcal disease (vaccine efficacy, 75.0%; 95% CI, 41.4 to 90.8). Vaccine

efficacy was maintained throughout the 4 years with no significant adverse events but no significant differences in mortality between the vaccinated and placebo groups. Pneumococcal vaccination does appear to prevent vaccine type strains causing infections in this older population over 4 years.

An updated Cochrane review in 2017 confirmed that pneumococcal vaccination provides significant protection against CAP in patients with COPD. The review included 12 studies totalling 2171 participants, with a mean age 66 years and with significant airflow obstruction (mean 1.2L from 5 studies & 54% predicted in 4 studies). Compared to control, vaccination reduced the risk of CAP (OR 0.59, 95% CI 0.41 to 0.85) with a number needed to treat NNT) to prevent 1 CAP of 19 (95% CI 13 to 52). A reduction in mortality was not seen in either all cause (OR 1.0) or from cardiorespiratory causes (OR 1.07) and there appears to be no preventative effect from hospital admissions. Vaccination appears to reduce the likelihood of an exacerbation of COPD (OR 0.60, 95% CI 0.39 to 0.93) with the NNT to prevent one exacerbation being 8 (95% CI 5 to 58). Although only one study directly compared the 2 available vaccines (23-valent PPV and 7-valent PCV) they found no difference in efficacy but describe a greater risk of some mild adverse effects with the 23-valent PPV vaccine.(167)

Current national and international guidelines advocate offering those with a diagnosis of COPD pneumococcal vaccination and annual influenza vaccination.(12, 68, 168)

CHAPTER 5: INHALED CORTICOSTEROIDS (ICS) and COPD

5.1 History of corticosteroids

Endogenous cortisone was first identified at the Mayo Clinic in the US in the 1920s, isolated in 1935 by a team led by Dr Edward Kendall when they identified it as important anti-inflammatory agent. It was subsequently synthesised in 1944 with Kendall going on to win the Nobel Peace Prize for Medicine in 1950.(169) Cortisone now has a wide range of therapeutic uses, both as an anti-inflammatory and immunosuppressive treatment.

In the late 1950s the use of oral corticosteroids revolutionised the care of asthma, another inflammatory condition of the lung, but it soon became apparent their long-term use led to significant unwanted systemic side effects. This led to the race to develop safer modes of (local) steroid administration and in the early 1970s the first inhaled corticosteroid (ICS) in the form of beclomethasone dipropionate (BDP) became widely available.(170) A newer understanding in the 1990s of the key role of inflammation in the development of COPD led to their widespread use in COPD.(171)

The underlying inflammatory nature associated with exposure to noxious agents (smoking, domestic fuel, dust etc) results in the development and disease progression in COPD (see section 2.2). With increased numbers of inflammatory cells, including, neutrophils, macrophages and T-lymphocytes found in the airways of people with COPD coupled with the clear success of corticosteroids in asthma treatment, led to the interest in their use in COPD.(13, 172)

Some early studies using oral corticosteroids in stable COPD showed some promising results with significant improvements in lung function but achieving improvements in FEV_1 of up to 50% does raise the possibility that the small sample (n=46) could have included patients with at least some underlying asthma, especially when the steroid responders also had greater bronchodilator reversibility. (173) This may highlight a problem we still face in clinical practice today i.e. that it is not always easy to differentiate between asthma and COPD or we often see people with both asthma and COPD. Finally, it is becoming clear that even with a firm diagnosis of COPD there are subgroups of phenotypes/genotypes who respond better than others to ICS and bronchodilators – so called ‘treatable traits”(174) and a one size fits all approach is being increasingly questioned. (175)

5.2 Mechanism of action of corticosteroids

Corticosteroids are lipophilic so are able to cross the cell wall membrane and bind with the glucocorticoid receptor or ‘chaperone’ in the cytoplasm. This combined molecule is then able to translocate into the cell nucleus where it binds to the glucocorticoid response element (GRE) at specific sites in the promoter regions of the target genes causing either suppression or stimulation of transcription (see figure 15). This resultant transrepression or transactivation both result from ribonucleic acid and protein synthesis. In transrepression, there is an inhibition of factors that control the production of pro-inflammatory meditators and inflammatory cells such as macrophages, eosinophils, lymphocytes and mast cells. In transactivation there is an increase in the expression of anti-inflammatory cytokines, e.g. interlukin10 (IL-10), or a downregulation of pro-inflammatory genes, e.g. IL-8. The lipophilic nature of corticosteroids allows them to remain in the cells and active even after they are undetectable in the plasma. (176, 177)

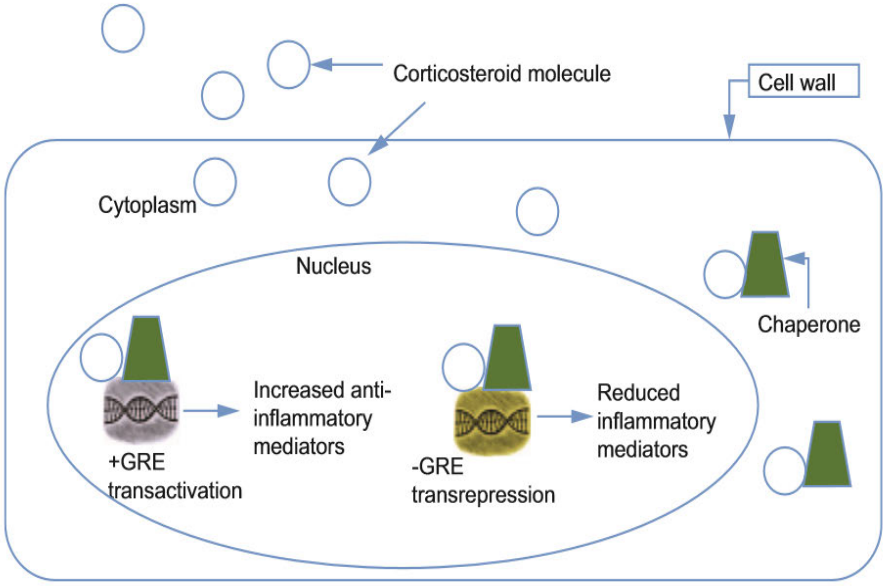


Figure 15: Mechanism of action of corticosteroids(177)

(GRE: glucocorticoid receptor element)

Corticosteroids not only have important anti-inflammatory properties in respiratory disease but have beneficial effects by upregulating β_2-adrenic receptors function to increase the response to these beta-agonist bronchodilators as well as reversing the downregulation of these receptors seen by chronic overuse.(177) This might partly explain why combining an ICS with a LABA has synergistic rather than additive effects (see figure 16).

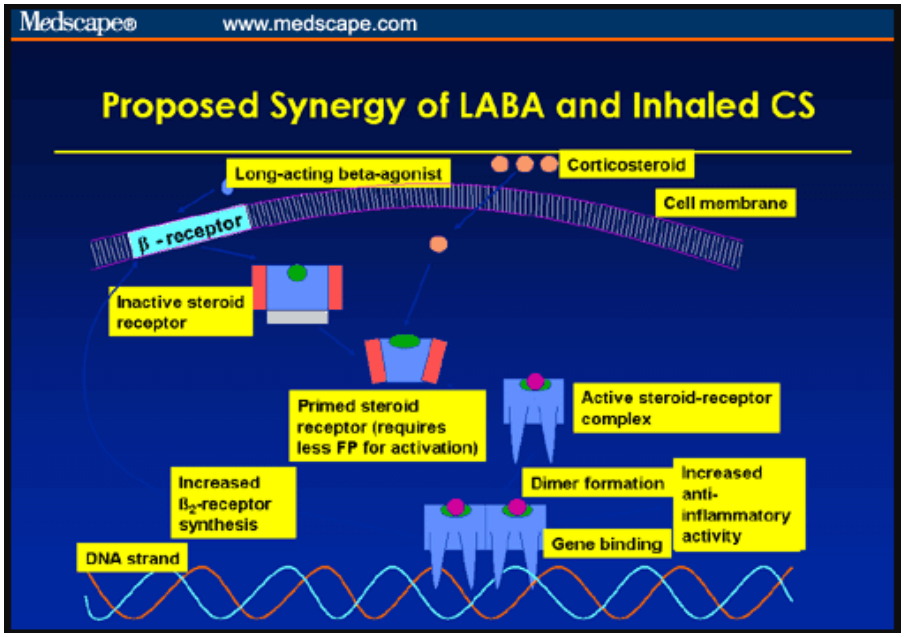


Figure 16: Proposed synergistic effect of LABA and inhaled corticosteroids.(178)

5.3 ICS in COPD

Early studies in the 1990s using an ICS in COPD demonstrated some indication of possible beneficial clinical effects but were inconsistent in their findings. In a short (2 weeks), 3-arm blinded study of 127 non-asthmatics with airflow obstruction comparing high dose beclomethasone to oral prednisolone and placebo, both oral steroids and ICS showed some similar rates of improved lung function which were consistently better than placebo. However these improvements in lung function did not reach some of their thresholds for statistical significance.(179)

In contrast, a group of 30 patients with chronic bronchitis, 20 were given 500µg of beclomethasone four times a day for 6 weeks and 10 were given placebo in a double blinded, randomised fashion. The treatment group demonstrated significant improvements in FEV_1 ($p=0.002$), FVC ($p=0.02$) and forced expiratory flow 25-75% ($FEF_{25-75\%}$) ($p=0.006$). Bronchial sample cell count, bronchial epithelial lining fluid albumin, bronchial fluid levels of lactoferrin and lysozyme, all markers of airway inflammation obtained by bronchoscopy, biopsy and bronchial lavage- all demonstrated statistically significant improvements in the ICS treatment group.(180)

In an 8-week, single-blinded study of 24 non-allergic, current smokers with airflow obstruction on spirometry, inhaled budesonide 1600µg per day was compared to placebo in a 50/50 split. Participants had to have had at least a 5-year smoking history, FEV_1 30-75% predicted with a negative bronchodilator and histamine provocation test, a negative skin prick test to 12 common allergens and a peripheral blood eosinophil count below 0.2×10^6/l. Participants kept a peak flow diary, including scores for cough, dyspnoea and sputum. Inhalers were weighed as a marker of treatment adherence when they returned every 2 weeks for bronchodilator reversibility, histamine challenge and citric acid cough challenges. Participants were given a 1-week wash out period before entry into the study to remove any existing inhaled treatments and could use as required Ipratropium during the study but no doses taken for at least 12 hours prior to their 2 weekly reviews. Although the authors noted a trend towards positive results in the ICS group, they were unable to demonstrate any statistically significant difference in parameters of lung function or airway responsiveness. They did demonstrate a significant reduction in self-reported dyspnoea scores in the budesonide group ($p<0.05$). (181)

These early studies had small numbers of patients, varied in length but were mostly of short duration; they used different doses of ICS and recruited slightly different groups of patients with different phenotypes and degrees of airways obstruction (FEV_1). This may account for the inconsistent results. However, overall, they suggested there could be a positive effect using ICS in COPD but that bigger, better designed and longer studies would be required to give a more definitive answer. The widespread use of ICS in COPD continued despite the lack of evidence.(182)

A larger, double blinded, placebo-controlled study was published in 1998. 281 COPD patients were randomised to receive inhaled Fluticasone 500µg or placebo twice daily for 6 months. Participants had to have obstructive spirometry with no significant reversibility (<15%) to salbutamol, at least a 10-pack year smoking history, at least one exacerbation requiring treatment in the preceding 3 years with chronic cough and sputum production. The two groups were well-matched at baseline, 49% being current smokers in both groups with a mean FEV_1 of 55% predicted in the placebo group and 59% in the fluticasone group. The treatment group had significantly less moderate to severe exacerbations (60% vs 86%, $p<0.001$), moderate defined as those requiring treatment by a doctor and severe exacerbations were defined as admission to hospital. FEV_1 significantly improved in the treatment group from 1.6L to 1.71L, a mean adjusted of 0.15L/9.4% ($p=<0.001$) as did FVC by an adjusted mean of 0.33L/5.6% ($p<0.001$). Symptoms scores, recorded by the patient in a daily diary, reduced significantly in the treatment group for cough ($p=0.004$) and sputum volume ($p=0.016$) but not for breathlessness. Those prescribed the ICS also had significantly improved 6-minute walk tests at 6 months compared to placebo (adjusted mean 27m vs 8m, $p=0.032$). The ICS were well tolerated with no significant side effects including serum cortisol suppression. However, this was a very heterogenous group of COPD patients and despite all having minimal reversibility to bronchodilators and a history of chronic bronchitis they had a FEV_1 which varied from 35 – 90% predicted, some being current and some ex-smokers with unreported exacerbations rates prior to entering the study. (183) With these caveats, this study not only demonstrated physiological but also clinical benefits that would be meaningful to a patient in potentially reduced exacerbations, reduced cough and sputum and with an increase in exercise tolerance.

Soon after this, 3 large important studies were published within a short period which all explored the role of ICS in COPD. Firstly EUROSCOPE, a randomised double blinded placebo-controlled study designed to evaluate the effect of inhaled budesonide 400 µg twice

daily over 3 years in a group of 1277 current smokers with mild COPD (mean FEV_1 77% predicted). During a 6-month run in period, all participants were given smoking cessation support including nicotine replacement therapy (NRT) and those who did not quit were able to enter the second 3-month phase where adherence to inhaled medication was checked by a hidden counter within the dry powder inhaler. They were only recruited into the main study if treatment adherence was $\geq$75%. Both groups were matched at baseline, 73% male with a mean age 52 years and a mean 39 pack-year smoking history The study was funded by Astra Draco a manufacturer of budesonide. The treatment group achieved the primary endpoint with a 40ml preservation in FEV_1 over the 3 years (p=0.05) compared to placebo. Initially there was an improvement in the treatment group and decline in the placebo group in FEV_1 but from 9 months to 3 years the rate of decline in FEV_1 was the same for both groups. The study did identify that those with a $\leq$36-year pack smoking history did seem to benefit more from an ICS with larger improvements in FEV_1 than those with a greater smoking history when compared to placebo (p=<0.001). No data was offered on exacerbation frequencies. Safety and side-effects were comparable in both groups, other than significantly more oral candidiasis, pharyngeal irritation/hoarseness and skin bruising in the ICS group. (184)

The second study in 2000, the ISOLDE trial, was a randomised, double-blinded, placebo-controlled, multi-centre trial over 3 years in the UK of 751 patients with moderate to severe COPD. It was funded by Glaxo Wellcome, a manufacturer of fluticasone with some of their employees sitting on the scientific and steering committees as well as undertaking data collection and analysis. The groups were matched at baseline with a mean FEV_1 of the cohort of 50% predicted, mean age 64 years, 38% smoked throughout the trial, approximately 25% females in both groups; no exacerbation histories were reported. The study's primary aim was to determine the long-term effect of fluticasone propionate 500 µg twice daily on decline in lung function. Secondary endpoints were, exacerbations, health status and side effects. The study was unable to show any significant reduction in the rate of annual decline in FEV_1 between the ICS and placebo groups (p=0.16) but did show a reduction in exacerbations from a mean per patient of 1.32/yr with placebo compared to 0.99/yr with ICS (p=0.026). The ICS group also had a significant slowing down in the decline in health status (p=0.0043). There was a small but significant reduction in mean cortisol levels in the fluticasone groups (p<0.032) but this was only present in 5% of the total fluticasone treated group and none had any signs of hypoadrenalism. Side-effect profiles were similar in both groups other than

higher number reporting oropharyngeal issues and skin bruising in the fluticasone group.(185)

Lastly, in 2000 the Lung Health Study reported a randomised, double blinded, placebo-controlled study of 1116 patients with COPD (mean FEV_1 68% predicted) comparing inhaled triamcinolone acetonide 600 µg twice daily to placebo. The mean age was 56 years, with 37% females, 90% were current smokers, smoking between 23-24 cigarettes per day. 56-61% reported daily cough or sputum. It was funded by the National Institutes for Health and was a multi-centre US study. The primary endpoint was decline in FEV_1. There was a mean duration of follow-up of 40 months with 3 monthly visits. There was no difference in the rate of decline in FEV_1 between both groups ($p=0.50$) but the ICS group did have a statistically significant reduction in respiratory symptoms (21.1 per 100 person-years vs. 28.2 per 100 person-years, $p=0.005$), visits to their physician secondary to respiratory issues (1.2 per 100 person-years vs. 2.1 per 100 person-years, $p=0.03$) and reduced airway reactivity in the triamcinolone group measured at 9 and 33 months by methacholine challenge ($p=0.02$ at both timepoints). At 3 years follow-up, there was statistically significant % reduction in bone density from baseline measured at the lumbar spine ($p=0.007$) and femur ($p<0.001$) in the triamcinolone group compared to the placebo group but the clinical significance of this is unknown. Adverse events and side effects were similar in both groups. (186)

Even in these large, multi-centre trials the inclusion criteria and participants vary significantly in terms of the severity of their lung function, age, smoking history, ethnicity and current smoking status with little reported on prior exacerbation history. Compounds and especially doses of ICS also varied within these studies but do suggest that it is a class effect and neither moderate or high doses had any impact on FEV_1 decline. As endpoints differed between each study and some were not always measured, there was no consistent results in relation to reduction in exacerbations or symptoms. However, they all consistently showed no benefit in reducing the rate of decline of FEV_1 compared to placebo.

Calverley et al in 2007 published results of a randomised, double blind trial with 4 arms comparing a combination inhaler containing the ICS, fluticasone and the long acting beta agonist, salmeterol (ICS/LABA combination); salmeterol alone; fluticasone alone; or placebo- in 6,112 patients who had COPD.(187) It's primary outcome was all cause mortality, and the study was powered accordingly and patients were followed up for 3 years. The groups were well-matched at baseline with a mean age of 65yrs, 76% males, 43% current

smokers with a mean of 49 pack-year smoking history. They had a mean of one self-reported exacerbation requiring antibiotics or steroids in the preceding year to recruitment. Their mean FEV_1 was 44% predicted with all having an FEV_1<60% predicted and <10% reversibility to albuterol with residual obstructive spirometry. Although there was a trend for the ICS/LABA to reduce mortality compared to placebo it did not reach statistical significance with a hazard ratio was 0.825 (95% confidence interval [CI], 0.681 to 1.002; p=0.052). The ICS/LABA combination compared to placebo did significantly reduce the risk of exacerbations with a rate ratio of 0.75 (95% CI, 0.69 to 0.81; p<0.001). Only in the ICS/LABA group did mean FEV_1 improve over the 3 years with a 29ml increase. All treatments arms showed improvement in mean St George's Respiratory Questionnaire (SGRQ) scores with the ICS/LABA showing the greatest with a mean 3-point improvement. However, is less than the 4-point clinically meaningful change.

In 2016, Vestbo et al reported on the SUMMIT study (188) of similar design to Calverley et al with 4 treatments arms containing the same classes of drugs or placebo as above. The primary outcome in this double-blinded, randomised, controlled study was again all cause mortality in a group of patients with mild to moderate COPD (FEV_1 50-70% predicted) but they also had cardiovascular disease or cardiovascular risk. The median follow up was 1.8 years (IQR 1.2-2.6). Compared to placebo, the ICS/LABA combination had no impact on all-cause mortality (hazard ratio [HR] 0·88 [95% CI 0·74–1·04]; with 12% relative reduction; p=0·137). The ICS/LABA had no effect on cardiovascular events, all treatments reduced the rate of moderate or severe exacerbations and a reduction in the rate of decline in FEV_1 by 8mls per year. There was no difference in pneumonia rates between the ICS arms and non-ICS arms.

Yang led a Cochrane review and meta-analysis in 2012 into the use of an ICS in COPD which included 55 studies with a total of 16,154 participants.(189) They found no evidence of mortality risk reduction (OR 0.98, 95% CI 0.83 to 1.16, 8390 participants) but a risk reduction for exacerbations (mean difference MD-0.26 exacerbations per patient per year, 95% CI -0.37 to -0.14, 2586 participants) and slowing down the rate of decline in health related quality of life measured by SGRQ (MD -1.22 units/year, 95% CI -1.83 to -0.60, 2507 participants). Risk of pneumonia was increased when using an ICS (OR 1.56, 95% CI 1.30 to 1.86, 6235 participants) as was oral candidiasis (OR 2.65, 95% CI 2.03 to 3.46, 5586 participants). The authors concluded that there were some potential benefits of using an ICS but these needed to be weighed up against the risks.

While the risk of ICS increasing pneumonias is widely accepted, care should be taken when comparing and evaluating studies as selection bias may play an important part in outcomes within studies and between studies, accounting for differences in mortality risk and incidence.(190)

5.31 Triple therapy inhalers – combinations of ICS+LABA+LAMA

2017 saw the licencing of the first 2 single inhaler triple therapy (SITT) containing formulations of an ICS, LABA and LAMA for the long-term treatment in COPD. This raised the possibility of potential improved efficacy compared to multiple inhaler triple therapy (MITT), reduction in the number of inhaler devices to simplify treatment regimens. Hopefully, improved adherence rates would translate into improved clinical outcomes as well as being more cost effective. SITT also provided options for clinicians and patients with once or twice daily preparations and pressurised metered dose inhalers (pMDI) or dry powder inhalers (DPI).

SITTs were not available locally to us in Wales, until the screening and recruitment for the TOWARD study had been completed. The evidence base for these is largely based on the following 5 studies which are also sponsored and designed by their manufacturers.

TRILOGY, a 52 week double blinded parallel randomised control trial was published in 2016.(191) It compared a twice daily SITT ICS/LABA/LAMA combination of beclomethasone dipropionate, formoterol fumarate and glycopyrronium bromide to a twice daily ICS/LABA combination of the same compounds in 1368 patients with COPD (mean FEV_1 36.2-36.9% predicted; all GOLD D and annual exacerbation rate 1.2/year). The primary endpoints were FEV_1 and Transition dyspnoea index (TDI). At week 26, the pre and post dose FEV1 had improved in the SITT compared to ICS/LABA group, by 0·081 L (95% CI 0·052-0·109; p<0·001) and 0·117 L (0·086-0·147; p<0·001), respectively. There was no significant difference in mean TDI scores between groups at week 26 (p=0.160). Adverse events were similar in both groups. Although a secondary endpoint, there was a reduction in severe-moderate exacerbations rates/year in the SITT arm of 0.41 vs 0.53 in the ICS/LABA, a rate ratio of 0·77 (95% CI 0·65–0·92; p=0·005).

The FULFIL study, a 24-week randomised, double blinded, double dummy study was published in 2017. It compared a once daily SITT containing fluticasone furoate/umeclidinium/vilanterol to a twice daily ICS/LABA containing budesonide/formoterol in 1810 patients with COPD (mean FEV_1 45.3%, 54% GOLD D with high symptom burden and frequent exacerbations but no detailed prior exacerbation rate published with 35% had no exacerbations in preceding year). The primary endpoints were FEV_1 and SGRQ at week 24. The SITT group achieved statistically significant improvements over the ICS/LABA group for both primary endpoints (both p<0.001) with the SITT group

achieving a 142ml improvement from baseline in FEV_1 (95% confidence interval [CI], 126 to 158) and 6.6 point improvement in SGRQ (95% CI, -7.4 to -5.7). Although a secondary endpoint, there was a reduction in severe-moderate exacerbation rates/year in the SITT arm of 0.22 vs 0.34 in the ICS/LABA, a rate ratio of 0.65 (96% CI: 0.49, 0.86, p=0.002).(192)

The TRIBUTE study, a randomised, double blinded, double dummy study was published in 2018 with the primary endpoint of severe to moderate exacerbations over 52 weeks.(193) 1532 participants with moderate severe COPD (FEV_1<50%)and $\geq$ 1 exacerbation in preceding 12 months, were randomised to receive either a twice daily SITT containing beclomethasone/formoterol/glycoperronium or once daily LABA/LAMA containing indacterol/glycoperronium . There was a reduction in severe-moderate exacerbation rates/year in the SITT arm 0.50 vs 0.59 rate ratio 0.848 (95% CI: 0.723, 0.995, p=0.043). (192) Adverse events were similar in both groups with no difference in pneumonia rates at 4% in both groups.

The largest study to date on SITT is the IMPACT study, a randomised double blind, parallel group study. It was published in 2018 with the primary endpoint of annual rate of severe or moderate exacerbations over 52 weeks. (194) 10,355 participants with COPD (FEV_1< 50% predicted + $\geq$ 1 exacerbation in preceding 12 months) were randomised to receive either a once daily SITT containing fluticasone furoate/umeclidinium/vilanterol, once daily ICS/LABA containing fluticasone furoate/vilanterol or once daily LABA/LAMA vilanterol/umeclidinium. There was a reduction in severe-moderate exacerbation rates/year in the SITT arm verses ICS/LABA rate ratio: 0.85, (95% CI: 0.80, 0.90, p<0.001), in SITT verses LABA/LAMA arm rate ratio: 0.75 (95% CI: 0.70, 0.81, p<0.001). Both of the ICS containing groups had a higher incidence of physician diagnosed pneumonia (hazard ratio, 1.53; 95% CI, 1.22 to 1.92; p<0.001). One secondary outcome of interest was the all-cause mortality which significantly reduced in the both ICS containing arms, with the SITT being statistically superior, with the hazard ratio 0.58 (95% CI, 0.38 to 0.88; 42% difference; unadjusted p=0.01) compared to the LABA/LAMA arm.

The ETHOS study, a randomised, double-blind, parallel-group trial, published in 2020 with the primary endpoint of severe or moderate CPD exacerbations over 52 weeks. (195) 8,509 participants with COPD ($FEV_1$$\geq$25-$\leq$65% predicted) and $\geq$ 1 exacerbation in the preceding 12 months) were randomised to either one of 2 dose ICS containing SITT containing budesonide/glycopyrrolate/formoterol, LABA/LAMA containing formoterol/glycoperronium

or ICS/LABA containing budesonide/formoterol, all twice daily. All ICS containing arms had lower exacerbation rates than the LABA/LAMA arm, with the higher 320µg ICS dose giving the best results with an exacerbation rate ratio 0.76, (95% CI: 0.69, 0.83, p<0.001). The incidence of pneumonias was higher in the ICS containing groups that than the LABA/LAMA group, 2.4-3% in ICS vs 1.4% in LABA/LAMA group (p<0.05 for all comparisons). One secondary outcome reported being all cause mortality with the therapy 320µg SITT group having 46% lower death rates than the LABA/LAMA group, 28 vs. 49 deaths (hazard ratio, 0.54; 95% CI, 0.34 to 0.87).

Care should be taken to compare the results from these seemingly similar studies. We'd be assuming a class effect of the individual drug compounds and probably more importantly, the study populations do vary in respect to severity of COPD and prior exacerbation requirements on study entry. These study participants are highly selected and were excluded if they had any significant co-morbidities so do not represent the typical real-world patients seen in every day practice, and usually with multiple comorbidities!(4)

Buhl et al reported the results of a 'real life' 1-year study comparing MITT to LABA/LAMA combinations in either a single or multiple inhalers.(196) It was a non-interventional, observational study recruiting patients with COPD who required any change in medication, recruiting 12,382 patients with 8,201 completing the 1 year follow up. Analysis was conducted using a matched-pair approach based on a broad range of unspecified demographic and disease characteristics. The LABA/LAMA combined inhaler group had fewer number of exacerbations compared to the MITT group (15.5% vs 26.6%; p<0.001) and also had the greatest improvements in quality of life scores as measured by CAT (mean ±SD -2.9±5.8 vs -1.4±5.5; p<0.001). Analysis by prior medication found the group going from a single to dual bronchodilator LABA/LAMA had the greatest improvement in CAT scores and the patients with the highest number of exacerbations were those going into the study on MITT and continued on a MITT on different combination. No data is offered on adherence rates to multiple inhalers. The authors raise the important issue of prior treatment when recruiting patients into studies. Suissa highlights this in relation to the reported mortality benefits of SITTs in both the ETHOS(197) and IMPACT(194) studies. He notes the mortality benefit was only apparent in the first 3 months of these studies and could be as a result of ICS withdrawal at randomisation. (198, 199)

To try and overcome these issues Suissa et al in 2022 reported a study using real life data from the UK GP-linked Clinical Practice Research Datalink (CPRD) that compared 4,106 ICS naïve patients with COPD going onto a SITT and 29,702 initiating a single inhaler dual bronchodilator LABA/LAMA. (200) Follow-up was 12 months with the main outcome being moderate (requiring prednisolone) or severe (requiring hospitalisation) exacerbations. Severe pneumonia and all-cause mortality were also reported. Both groups were matched at baseline for age (mean 70yrs), gender, current smokers (54%), obesity, blood eosinophil count (mean 3-3.1%), FEV_1 (mean 60% predicted). 43% of the SITT group had no reported exacerbations in the year preceding the study. The rate (per 100/year) of moderate or severe exacerbations in the overall SITT group was greater than the LABA/LAMA group, 64.8 vs 59.1 with an adjusted hazard ratio (HR) 1.08 (95% confidence interval (CI): 1.00–1.16). However, there was a benefit of SITT vs LABA/LAMA on exacerbations in those who had $\geq$2 exacerbations in the year preceding study entry, HR 0.83 (95% CI: 0.74–0.92), history of asthma 0.86 (95% CI: 0.70–1.06) or an eosinophil count > 300 cells/µL, HR 0.89 (95% CI: 0.76–1.05). Relative to the LABA/LAMA group the HR for severe exacerbations was 1.32 (95% CI: 1.13–1.55), for severe pneumonia 1.50 (95% CI: 1.29–1.75) and mortality 1.53 (95% CI: 1.30–1.79). This study supports current guidelines (12, 68) on using an ICS in addition to a dual bronchodilator in those patients with a history of 2 or more exacerbations per year, asthma or a higher eosinophil count > 300 cells/µL and that there is an increased risk of pneumonia.

5.32 Single combination inhalers verses multiple inhaler devices in COPD

Researchers have for some time explored the possibility that combination inhalers might improve adherence and result in improved clinical outcomes and that conversely poorer adherence results in poorer outcomes.

In 2011 Yu et al published a US study of 2 matched groups of 11,747 patients with COPD prescribed either a single combination inhaler or multiple inhalers over a 12-month period.(201) Groups were matched for drug class and numbers of prescriptions filled. Data on healthcare claims was extracted from the combined database of the Thomson MarketScan Commercial Database and MarketScan Medicare Supplemental and Coordination of Benefits. Results were controlled for potential confounding factors and the small number of baseline differences were controlled in a multivariant regression analysis. They found the multiple inhaler group had a 40% greater risk of any type of exacerbations (adjusted HR = 1.40, 95% CI at 1.34 to 1.46, $p < 0.0001$). The multiple inhaler group had significantly more hospital admissions ($p<0.0001$), inpatient days ($p<0.0001$), urgent care visits ($p=0.0026$), outpatient visits ($p<0.0001$), and other medical service visits ($p<0.001$). Healthcare costs were significantly higher in the multiple inhaler group ($p<0.0001$). This study raises the question that there could be some synergistic effect in putting the same type of therapies into one device and the benefits are not related to adherence in a well-matched population taking the same classes of drugs. This is on the assumption that there is no clinical difference between compounds as no breakdown on inhaled drugs (just classes) was given in this study.

INTREPID, published in 2020, is a real world, multicentred, open label, randomised study comparing triple therapy (ICS+LABA+LAMA) either by SITT or MITT in 3092 patients with COPD.(202) The primary outcome was the number of positive responder ($\geq$2 points) using CAT at 24 weeks and the two groups matched at baseline. The proportion of positive responders on CAT was greater in the SITT than MITT group (OR 1.31, 95% CI 1.13–1.51; $p<0.001$) and they also experienced a +50ml difference in FEV_1 (95% CI +26 to +73 mL; $p<0.001$. The number of patients having at least one critical error in inhalation technique at week 24 was not significantly different between groups (6% in the SITT group, 3% in the MITT group; OR 1.99, 95% CI 0.87–4.53; $p=0.103$). Adverse events including pneumonia were similar in both groups. No measures of treatment adherence were reported.

Bogart et al published a US retrospective cohort study in 2020 in patients with COPD prescribed a SITT or MITT.(203) They used data collected from a large insurance claims database with the start date for each patient being the date of first initiating SITT or all components of MITT with follow up data collected for 12 months. Adherence was measured using proportion of days covered (PDC) by supply of their treatment, good adherence a PDC $\geq$0.8 and Persistence defined as duration of treatment from time from initiation to discontinuation ($\geq$60 days gap between prescriptions classed as discontinuation). The SITT group had significantly higher PDC (mean [median]: 0.66 [0.74] vs 0.48 [0.44]; p<0.001) with more having good adherence (46.5% vs 22.3%; RR [95%CI]: 2.08 [1.85–2.30]) at 6 months. Persistence was longer in the SITT group (325 vs 90 days) and they were twice as likely to be persistent at 12 months. PDC values were similar at 12 months (mean [median]: 0.60 [0.74] vs 0.40 [0.32]) as was adherence (43.2% vs 17.4%; RR [95%CI]: 2.48 [2.00–3.01]). In this cohort having a single inhaler verses multiple did seem to have a positive impact on adherence.

Halpin et al in 2022 compared adherence and persistence in 2 well matched groups of patients with COPD, one prescribed SITT and the other MITT.(204) Data was collected retrospectively from systems linking primary care (Clinical Practice Research Datalink Aurum) and secondary care (Hospital Episode Statistics [HES] Admitted Patient Care). Patients were aged $\geq$35 years and had obstructive spirometry ($FEV_1/FVC<0.7$). An inverse probability of treatment weighting was used to balance any baseline characteristics between groups. Adherence, the primary endpoint, was measured using proportion of days covered (PDC) by supply of their treatment, good adherence was defined as a PDC $\geq$0.8 and persistence measure using a gap of >30days to refill a prescription as a marker of non-persistence. The SITT group had significantly greater adherence at 6, 12 and 18 months compared to MITT (p<0.001 for all timepoints) and median persistence rates were also higher with SITT (5.09 months vs 0.99 months). Patients who switched from MITT to SITT had showed improved persistence (0.5 to 0.78), including those with low adherence (PDC<0.5) improving from 0.31 to 0.74 and those with higher adherence, improving from 0.73 to 0.83.

A recent Spanish study set out to determine not only if SITT improved persistence but also if this impacted on exacerbations and health care utilisation.(205) This retrospective, real world observational study used analysed health records of patients over 40 years old with a diagnosis of COPD who had been initiated on either SITT or MITT between 01/06/2018 and 31/12/2019. They analysed data on medication /inhaler persistence (allowing up to 60 days

without a prescription refill), exacerbations, health care utilisation and health care costs 12 months from initiating therapy. The groups had comparable age, gender, BMI, smoking history, comorbidities, lung function severity grading, eosinophil counts and exacerbation history in preceding year (approximately 53% no exacerbations; 33% one exacerbation & 14% $\geq$2 exacerbations). The SITT group had a significantly higher number of severe exacerbations (required hospital admission) in the preceding year, 0.37 vs 0.30 (p=0.028). The results included 1,011 in the SITT group and 3,614 in the MITT group. Persistent rates were higher in the SITT verses MITT group at 6 months (80.6% vs 76.7%, p=0.008) and 12 months (62.4% vs 53.8%, p<0.001). Patients initiating SITT had a lower exacerbation risk (HR = 0.68; 95% CI = 0.61-0.77; p=0.001) over the following year. The mean number of exacerbations was significantly lower in the SITT group (0.56 vs 0.71; p < 0.001) compared to MITT with a lower proportion with 1 or more exacerbation (p<0.001), lower proportion with moderate exacerbations (p=0.031) or severe exacerbations (p=0.002) and a longer time to the first exacerbation (203.3 vs 179.3 days; p<0 .001). The SITT group also had a reduced mortality risk at 12 months, 2.9% vs 4.4% (HR = 0.67; 95% CI = 0.63-0.71, P = 0.027). SITT was associated with significantly reduced COPD related health care resources with reduced primary care visits (8.2 vs 10.5; p<0.001), reduced specialist care (1.0 vs 1.1; p=0.044), emergency room visits (0.5 vs 0.7; p<0.001), hospitalisations (11.4% vs 15.4%; p=0.001), length of hospital stays (2.0 vs 2.6 days; p=0.026) when compared to MITT. It was estimated this resulted in a mean adjusted cost saving €403 (€2,520 vs 2€,923; p=0 .006) over the following year.

All these studies base adherence on inhaler pick-ups and not recorded inhalations in real time which is feasible with new e-inhalers.

5.4 Cost of inhaled medications for COPD

With COPD and other respiratory diseases (e.g., asthma) being common, the cost of treating them with respiratory medicines (inhalers) is significant. The tables below illustrate the costs of the most commonly prescribed inhalers for COPD in Wales, at the start of the study in 2017. (206)

Table 1: Breakdown of inhaler costs

	30-day cost (£)	**Annual cost (£)**
Seretide Accuhaler (licensed) LABA/ICS	35	420
Seretide pMDI (unlicensed but widely used) LABA/ICS	59.48	714
Fostair 100/6 LABA/ICS	29.32	352
Spiriva Handihaler LAMA	33.5	402
Spiriva + Seretide LAMA+LABA/ICS	68.5 - 93	822 – 1116
Spiriva + Fostair LAMA +LABA/ICS	62.82	754
Anoro / Duaklir / Spiolto / Ultibro LABA/LAMAs	32.5	390

Potential inhaler savings per patient per year range between £364-£726 per year and if only 100 patients were switched from Spiriva & Seretide and maintained on a LABA/LAMA for 1 year, with no change in exacerbations or health care utilisation – then that organisation would potentially save between £36,400- £72,600 per year. Many of these 100 patients will be prescribed these inhalers for the rest of their lives, typically for 10-30 years saving the organisation between £360,000 to over £2.1M over this period!

5.5 Why ICS withdrawal in COPD

This section is a focus point of the thesis as it builds on study rationale. I undertook a literature review using PubMed, Medline, Cochrane database, CINAHL and EMBASE. We used the following MeSH subheadings in searches:

- COPD
- COAD
- Chronic obstructive pulmonary disease
- Chronic obstructive airways disease
- Emphysema
- Chronic bronchitis
- ICS
- Inhaled steroid
- Inhaled corticosteroid

Searches were limited it to English text and the years 1972 to present -2023. Papers were screened according to titles and full text documents on certain key studies including FLAME, list 3 were selected.

International guidelines for the management of patients with COPD currently recommend the addition of inhaled corticosteroids (ICS) in combination with acting beta agonist (LABA) therapy as second line treatment usually to those already receiving long-acting muscarinic antagonist (LAMA) and in people with severe to very severe COPD and a history of recurrent exacerbations. (37) ICS are effective anti-inflammatory agents in asthma but appear much less effective in COPD, a predominantly neutrophil driven disease. Early studies suggested some clinical benefit from adding an ICS to short acting bronchodilators (185) but although longer term clinical studies such as TORCH showed a reduction in exacerbations (185) there was no statistical difference in its primary endpoint of mortality above placebo and moreover, ICS monotherapy was no more effective than a twice daily LABA. Several clinical studies of ICS monotherapy have been revaluated in a meta-analysis (185), a Cochrane review (207) and literature reviews (208) - all concluding there is no convincing clinically meaningful benefit of ICS in preventing /reducing exacerbations or improving quality of life in *stable* COPD.

Further, the use of ICS has been associated with local and systemic side effects, including skin thinning and easy bruising, (209) oral candidiasis, (209, 210) increased risk of pneumonia,

(209-212) osteoporosis, early onset diabetes, cataracts, (209) and tuberculosis. (213) The TORCH study itself demonstrated more side effects than placebo and LABA alone-particularly increased pneumonia risk that was statistically significant and clinically important. (211)

It is important to note that sub-group analysis of TORCH and other studies suggest that ICS may benefit some groups of patients. (210) Certain COPD phenotypes e.g. characterized by repeated exacerbations (214), inflammatory patterns (215) and co-morbidities (216) may respond differently to ICS.

However, in clinical practice, ICS are widely prescribed for the majority of COPD patients, many of whom do not fall into these high risk categories. (217) A study of prescription drugs from UK general practices suggests that over 37% of COPD patients were over-treated (according to GOLD 2013 recommendations) and, of those, 96% were over-treated with ICS. (218) The largest and most recent database study to date in the UK reported approximately 50% of COPD patients in exacerbating and non-exacerbating cohorts were all receiving ICS, either in combination with a LABA (26.7%) or a LABA and LAMA (23.2%). So-called triple therapy with ICS + LABA + LAMA was the most frequently used treatment even in GOLD Groups A and B i.e., even in those who had no exacerbations in the previous year, 49% were still prescribed ICS. (219)

LABAs and LAMAs are effective in improving air flow by reducing hyperinflation, reducing mucous secretion and even some anti-inflammatory effects so can be effective in preventing exacerbations in their own right (220). Combined LABA+LAMA formulations have been shown to be superior to individual components in improving lung function, quality of life and reducing exacerbations with no increased side effects (220-223) and should be considered in breathless patients not responding to short acting bronchodilators. These combination inhalers are not yet specifically mentioned in the guidelines although the LABAs and LAMAs prescribed alone or in 2 separate inhalers are.

The well-powered WISDOM study randomized 2,485 patients with moderate to severe COPD (FEV_1<50% predicted) and who had at least 1 exacerbation in the preceding 12 months to either a continuation of high dose ICS (fluticasone 500 mcg daily) or to ICS withdrawal to 0 mcg over 12 weeks (both groups remained on a LABA/LAMA combination). There was no difference in the primary endpoint of time to first exacerbation, number of exacerbations or

quality of life over the following year but there was a drop in FEV_1 of around 60 ml. (224) Although the patients did not appear to notice this symptomatically, the importance of this change in lung function is unknown.

Abrupt withdrawal of ICS in COPD has been associated with an increased risk of exacerbations (ISOLDE) (225). However, a more recent, larger randomized controlled study (FLAME) of 3,226 patients with moderate to severe COPD and at least 1 exacerbation in the last 12 months stopped ICS abruptly (stabilized on LAMA alone for 1 month) then randomized 1:1 into either a LABA/LAMA combination or ICS/LABA combination inhaler. The dual bronchodilator appeared as good as or better than the leading high dose ICS/LABA combination in reducing exacerbation rates and the time to first exacerbation, irrespective of severity of lung function, age, smoking and prior ICS use. (226)

CHAPTER 6: sTep dOWn inhAlers in the Real worlD (TOWARD)

6.1 Rationale

In summary, current guidelines (37) for the management of Chronic Obstructive Pulmonary Disease (COPD) recommend treatment with inhaled corticosteroids (ICS) in combination with long-acting beta-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs), for people with recurrent exacerbations and moderate to severe obstructive lung function. However, the beneficial effects of ICS in many people with COPD remain under debate, their side-effects are well documented and prescribing cost are considerable.

Some randomised controlled studies (224, 226) suggest withdrawing an ICS is not associated with increased exacerbations and LABA+LAMAs alone may show superior efficacy to ICS/LABA combinations. (see section 4.15) The feasibility and effects of stopping ICS in a real-life setting in stable patients and the use of shared decision making to facilitate withdrawal in a general population of COPD patients, have not been tested.

6.2 Study design

This is a real-world study. We did not do a randomised study as we were exploring the feasibility and patient choice and felt unethical to deny 50% of our patients the option to choose their own inhaler. Moreover, with small number any randomisation may lead to unequal distribution of a confounding factor e.g. people in any intervention arm may by chance all have very severe or be on the same inhaler. We did not do multicentre study which would provide greater external validity as we did not have the resources. We did not do intention to treat analysis as the patients were free to go back to any inhaler or combination at any point. Our main outcomes were based on those who remained off an ICS as opposed to those who restarted ICS (irrespective of their original choice i.e retrospective review of prospectively gathered data)

6.3 Primary aim

A feasibility study to establish whether a future, definitive intervention study of removing ICS from a triple combination inhaled regimen for people with stable COPD, is feasible and safe, in the real world.

6.4 Primary Objectives

Feasibility was tested according to predefined criteria using the ACCEPT (Acceptance checklist for clinical effectiveness pilot trials) Model.(227) This Model breaks studies into smaller critical components of success (feasibility) and suggests ways each can be monitored and evaluated. At the end of the study, a decision can then be made either to accept each component as satisfactory or amend when unsatisfactory for it to work in a larger study. Both of these would inform the decision to proceed to a full study or if a component is unsatisfactory and cannot be amended to inform the decision *not* to proceed to a larger study. This allows for a structured assessment of each critical component covering three broad areas:

-feasibility and appropriateness of trial design

-feasibility and appropriateness of the mechanics, management and safety of interventions

-acceptability and efficiency of implementing the research procedures

Our predefined aims were:

1) Sample size and participants:

• 95% or more of health care professionals working with the participating study team agree to take part in the study

• Acceptable recruitment rate with >50% or more of eligible patients consenting to participate

• Follow up data for primary outcomes can be collected for >60% or more of the enrolled patients

2) Interventions:

• >80% of eligible health care professionals signed up to the study to receive the allocated formal training in applying a patient-centred inhaler switch

• 80% of subjects remain compliant with the intervention (i.e. inhaler switch/step down) during the intervention period

3) Outcomes:

• Overall mean number of exacerbations is not 20% more than baseline
• > 60% return rate of QoL questionnaires
• QoL is not worse in >49% participants
• > 50% compliance with return of economic analysis data collection tools
• Inhaler costs reported in the intervention period are equal to, or better than, those reported during the same period in the conventional management period

All feasibility criteria were tested with a view to a) refining the process and b) to inform the choice of outcomes for the main study. Other outcomes following clinical, pathological, quality of life (QoL) and health economics data were also recorded as part of the feasibility criteria as well as secondary objectives within the clinical component of the study:

a) EuroQol-5D (EQ-5D) and COPD assessment test (CAT) quality of life tools (228, 229)
b) Moderate-severe exacerbation rates (need for antibiotics +/- oral steroids or attendance to hospital for COPD)
c) Time interval between inhaler switch and first moderate-severe exacerbation (days).
d) Datasets for inhaler prescriptions, QoL and health care contacts to include:
    a. Number exacerbations, days in hospital, time to first exacerbation
    b. Total inhaler costs
    c. Estimates of total cost effectiveness.

If successful, this pilot would inform a larger more definitive study whose Primary Outcome would be e.g. based on:
"The proportion of patients with stable COPD who can be successfully switched from triple inhaled therapy (ICS+LABA+LAMA in any combination of inhalers) to dual inhaled bronchodilator therapy (LABA+LAMA) and maintained on this for 12 months."

6.5 Secondary objectives TOWARD study

1. Comparison of the number of moderate and severe exacerbations in those on LABA+LAMA over 52 weeks compared with their previous 52 weeks on LABA+LAMA+ICS
2. Comparison of the number of moderate and severe exacerbations in those on LABA+LAMA over 52 weeks compared with those reverting back to triple therapy (LABA+LAMA+ICS)
3. Comparison of time to first exacerbation in those on LABA+LAMA over 52 weeks compared with those reverting to triple therapy (LABA+LAMA+ICS)
4. Proportion of patients requiring restarting ICS (on the discretion of their clinician) at each visit
5. Comparison (trend) of CAT, EQ-5D, FEV_1 at 0, 4, 12, 26 and 52 weeks between those on LABA+LAMA versus those reverting back to triple (LABA+LAMA+ICS)
6. Proportions of patients choosing each LABA+LAMA device and their reasons why
7. Comparison of total inhaler prescription costs 1 year prior and 1 year after switch

6.6 METHODS

Study design

This was an open label, interventional, cohort, feasibility study.
As a real-world study there was no blinding which was felt important when it came to patient choice of treatment, co-production and potentially adherence to treatment. Inclusion/exclusion criteria were minimal so as not to exclude the typical patient seen with multiple co-morbidities usually excluded from large randomised trials but their results often extrapolated to include. We did not do a randomised study as we were exploring the feasibility and patient choice and felt unethical to deny 50% of our patients the option to choose their own inhaler. Moreover, with small number any randomisation may lead to unequal distribution of a confounding factor e.g. people in any intervention arm may by chance all have very severe or be on the same inhaler. We did not do multicentre study which would provide greater external validity as we did not have the resources. We did not do intention to treat analysis as the patients were free to go back to any inhaler or combination at any point. Our main outcomes were based on those who remained off an ICS as opposed to those who restarted ICS (irrespective of their original choice i.e retrospective review of prospectively gathered data). A feasibility study was important to test issues such as safety, recruitment and quality of data but also to potentially inform a power calculation for a larger study.

6.61 Ethics and Regulatory Considerations

The research proposal was reviewed and approved by its sponsor, Hywel Dda University Health Board Research and Development Department prior to submission for Research Ethics Committee permission (Wales REC 7 reference 17/WA/0009). I applied for the Ethics approvals in 2017, attended the meeting, answered their questions, reviewed their finding and resubmitted after making the necessary revisions in order to get approval. Prior to submission, the study design and concept were discussed at a local Breathe Easy Group who largely seemed supportive and did not result in any significant change to the protocol.

Hywel Dda provided governance oversight for the study including being monitored and audited by its research governance department with no major issues identified. The study was registered on ClinicalTrial.gov (NCT03527927).

A major amendment to the protocol was approved by Research Ethics Committee in May 2019 (Wales REC 7 reference 17/WA/0009), again led by myself.

(See Appendices 1-3 for study approvals)

6.62 Participants

Potential participants with a diagnosis of COPD were recruited from a combination of hospital clinics and primary care practices across Carmarthenshire between May 2017 and August 2019. Local Primary Care Practices were approached to gain consent to participate in the study. Potential participants were identified through a combination of hand searches or use of an electronic search tool. Patient Information Sheets (see appendix 4) would be handed to or mostly posted out to potential participants before being followed up by a telephone call after a minimum of 48 hours. If they were interested when telephoned, then the researcher would undertake a simple screening to exclude any obvious exclusion criteria (for example, no smoking history, history of asthma, current inhaled medications). Potential participants were then invited for formal screening, consent, and completing their first visit either at a hospital site or at their primary care practice. Subsequent study visits were also carried out at the same site whenever possible.

Participants with an existing diagnosis of COPD were screened using the following inclusion and exclusion criteria.

Inclusion Criteria

- Diagnosis of COPD (as defined by the General Medical Services Quality and Outcome Framework) (230)
- Current or ex-smokers with at least a 10-pack year smoking history
- Aged 40 years old or greater
- Post bronchodilator FEV_1 <80% predicted and FEV_1/FVC <70%
- Prescribed a combination of an ICS, LABA and LAMA
- Any comorbidity was allowed except dementia or severe life-limiting illness (see below)

Exclusion Criteria

- Unwilling or unable to sign informed consent
- Features suggestive of asthma on screening (previous asthma diagnosis, large variability in symptoms, atopy, nasal polyps, <10 pack year smoking history, peripheral blood eosinophilia >600mm^3)
- Recent moderate or severe exacerbation of COPD within last 6 weeks (antibiotics or oral corticosteroids or hospitalisation >24 hours)
- Inability to use inhaler devices
- Life expectancy < 1 year

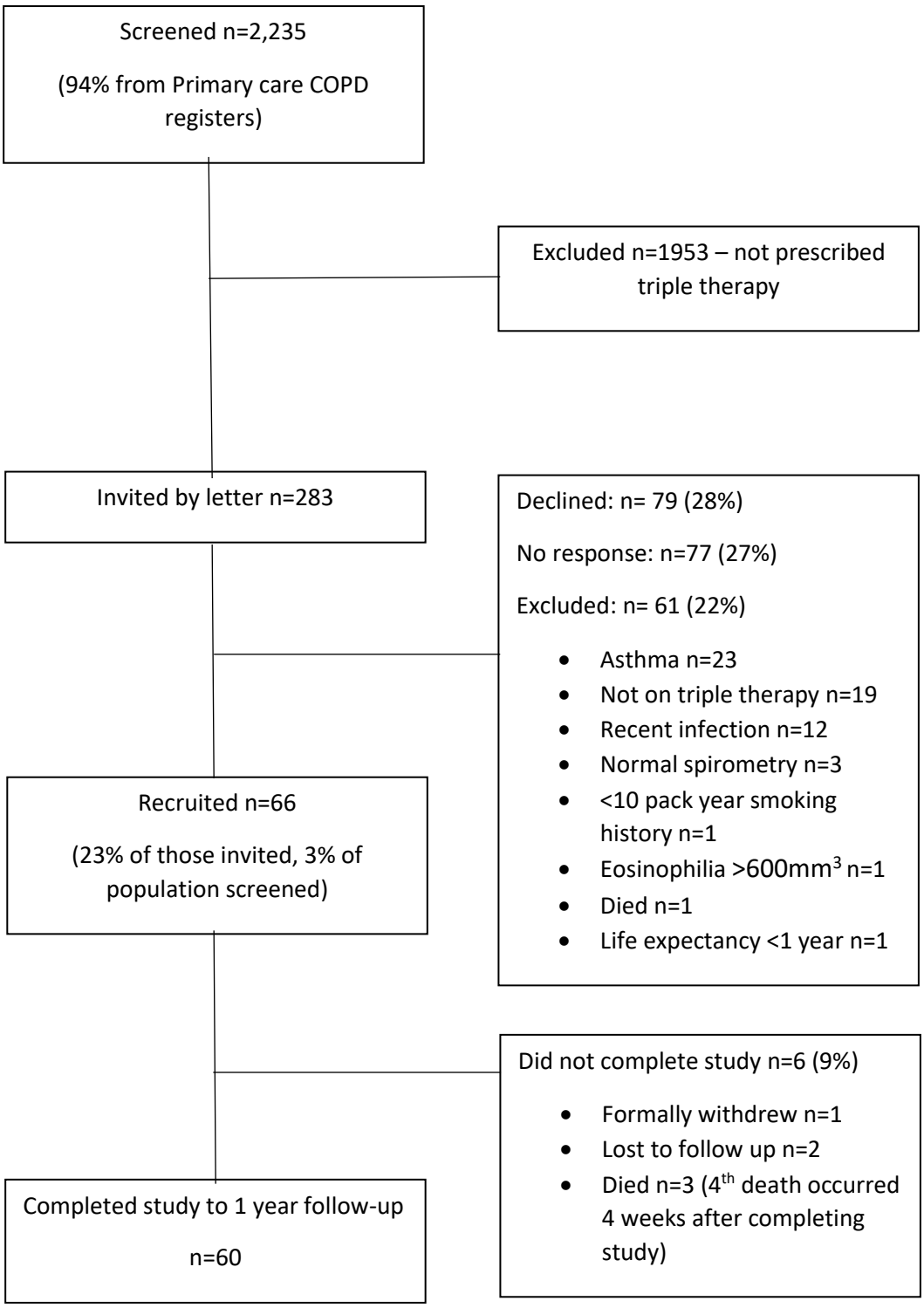
6.63 Recruitment

We screened 2,235 patients, 94% from primary care systems with the remainder from hospital chest clinic records. (See figure 17 Consort diagram) Most were excluded as they were not prescribed any triple therapy leaving 283 invited to participate.

Over half either declined or did not respond to the invitation letter. A further 22% (n=61) did not meet the inclusion or exclusion criteria with 24 having asthma or atopy, 3 having normal spirometry and a further 19 not prescribed triple therapy when re-screened for up-to-date prescribing. We recruited 23% of those who had an invitation letter or 3% of the entire population on our COPD databases.

We recruited 66 people (83%) from the target of 80 patients over 16 months.

Figure 17: Study consort diagram



6.64 Procedure (see Figure 18):

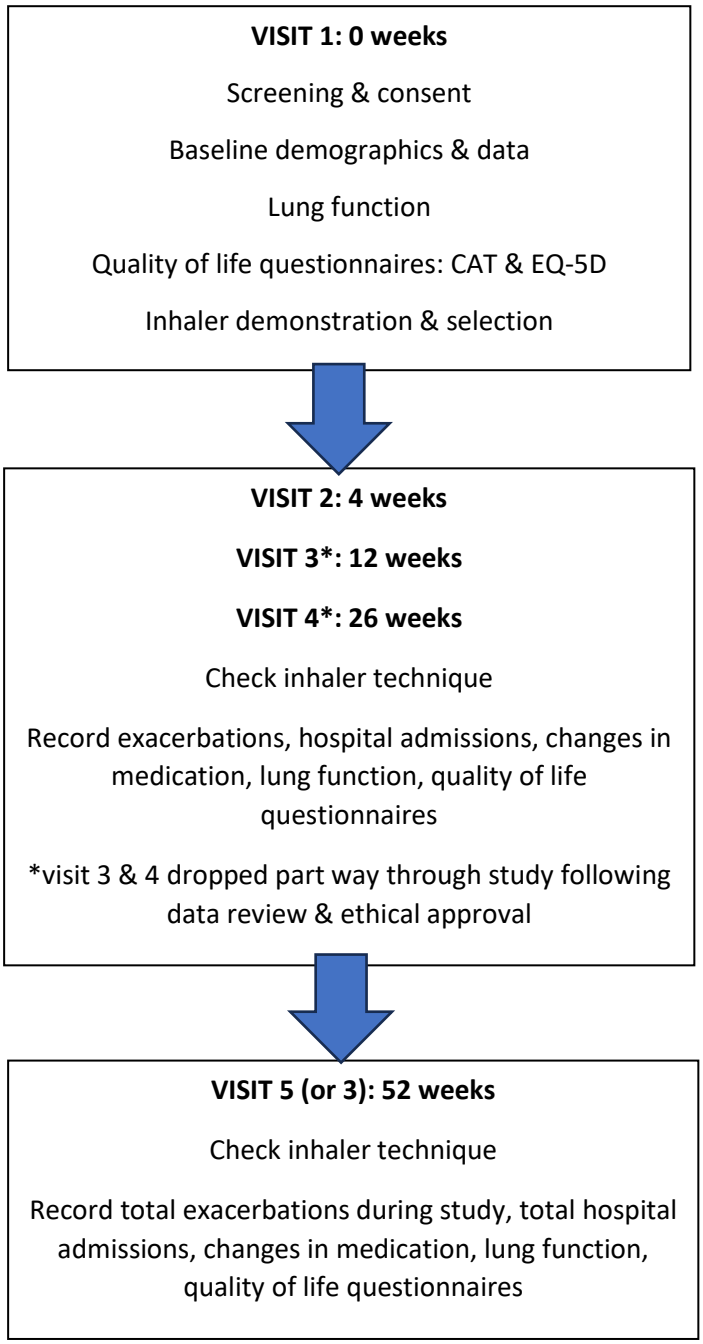
Visit 1

80% of assessments were conducted in a hospital clinic room and the remainder in primary care. All assessments were undertaken by the Principal Investigator.

The purpose of the study was again explained, and opportunity given to ask questions, reinforcing that participation was voluntary and even if consent was given, it could be withdrawn at any time without explanation or impact on future treatment or ability to participate in other research. Following further screening using the inclusion and exclusion criteria, informed consent was gained using the approved documentation (see appendix 5). The patients' GPs were informed of their participation and could continue to treat without restrictions if or when they may present (see appendix 6).

Baseline data was recorded as per protocol (see appendix 7) including medication history, exacerbation history, smoking status, social circumstances and medical history. Height and

Figure 18: Study flow chart



lung function were measured (on Carefusion MicroLab ML3500 MK8 Spirometer) according to ARPT standards(231) as well as quality of life questionnaires completed.

The four (single-use) placebo device options for the current LABA/LAMA licensed inhalers (see figure 19) were shown to each participant and they were encouraged to try each one.

Once they had tried the four placebo devices and chosen a device, further instruction on use and care of the device was given with reference to the written instructions included with the dispensed active device. Adequate inhaler technique had to be demonstrated otherwise an alternative device had to be chosen with an explanation why. Once chosen they were asked why they had chosen that device and reason or reasons document.

They were told that although 'drug molecules' differed slightly, that there was no documented proven difference in their clinical efficacy with the difference being in the way the drugs were delivered. The 4 main differences were explained using a prompt script to reduce the risk of researcher (conscious or unconscious) bias:

- Once (Breezhaler, Ellipta, Respimat) versus twice (Genuair) daily dosing
- Dry powder (Breezhaler, Ellipta, Genuair) versus soft mist (Respimat)
- Needing to load (Breezhaler) each dose versus preloaded (Ellipta, Genuair, Respimat)
- Visible dose counter (Ellipta, Genuair, Respimat) versus none (Breezhaler)

Fig 19: The 4 device choices used in TOWARD. (232)

	Breezhaler – dry powder
	Ellipta – dry powder
	Genuair – dry powder
	Respimat – soft mist

Visit 2, 3, 4 and 5 (4, 12, 26 and 52 weeks)

Spirometry, quality of life questionnaires (EQ-5D, CAT), smoking status were repeated, any changes to medications and reasons for any change were also documented, including any switch of inhalers.

Participants were also asked about any (self-treated) exacerbations (exacerbation packs), attendances to their GP or hospital attendances/ admissions since the previous visits. Healthcare contacts were cross checked on our electronic patient information systems (Welsh Clinical Portal, Welsh Patient Administration System) and access to primary care records (EMIS, Vision).

Inhaler technique was re-checked and instructions given on improving technique where required.

Following interim data analysis and Ethics amendment, visits 3 and 4 were dropped from the protocol in May 2019, 2 years into the study, as they were felt to be quite onerous to the patients and added no additional meaningful data.

All visits were conducted by myself only.

The hospital records were sent to an independent physician to investigate whether any participant death could have been related to the study.

The inhaler cost analysis was calculated using the published NHS inhaler prices for 2016. (206)

6.65 Baseline characteristics (see table 2)

Of the 66 recruited from a target of 80, 23 were female (35%), 43 males, all with a mean age of 70.4 years old (+/- 7, range 53-83). The mean FEV_1 % predicted was 48.7% (+/-15) suggesting significant moderate to severe airflow obstruction resulting from a mean smoking history of 42 pack years (+/-19, range 10-120).

In the year prior to study entry, recruited patients had a mean of 1.6 exacerbations (+/- 2) but very few hospitalisations with a mean of 0.05 (+/- 0.2) per patient.

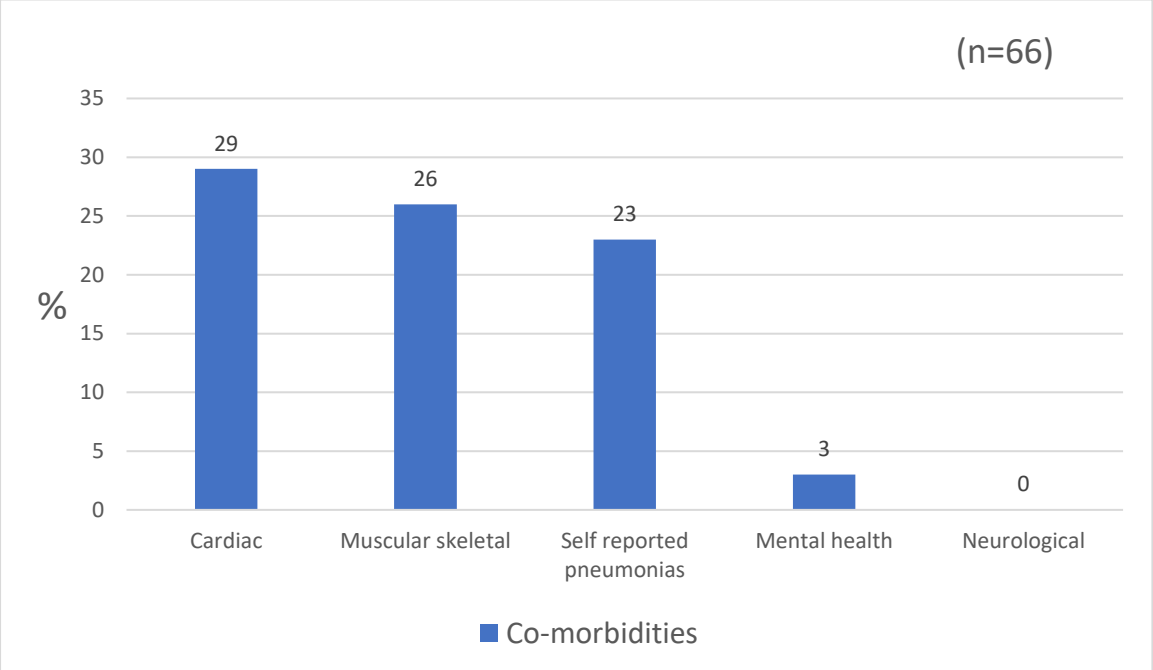
They were highly symptomatic with a mean CAT score 22.6 (+/-8) and limited by their breathlessness with a mean MRC dyspnoea grading 3.3 (+/-1).

12 (18%) were current smokers, 82% ex-smoker and 4 (6%) had LTOT. 14 (21%) lived alone and nobody lived in a residential or nursing care home. Co-morbidities and history of pneumonia were common (see figure 20).

Table 2: Summary of baseline cohort characteristics

Variable	Mean	Standard Deviation
Age	70.4 yrs (range 53-83)	+/- 7
Pack years	42 (range10-120)	+/-19
FEV1 % predicted	48.7	+/-15.0
MRC dyspnoea scale	3.3	+/-1.0
CAT score	22.6	+/-8.0
Eosinophil count (highest recorded)	0.3	+/-0.1
Moderate/severe exacerbations (year preceding study)	1.6	+/-2.0
Hospital admissions (chest related, in preceding year)	0.05	+/-0.20

Fig 20: Frequency of Co-morbidities and history of pneumonia at baseline (based on questions and medical records)



6.7 RESULTS

Data was analysed using version 26.0 of the IBM SPSS statistics package.

6.71 Primary outcome: FEASIBILITY of a larger trial

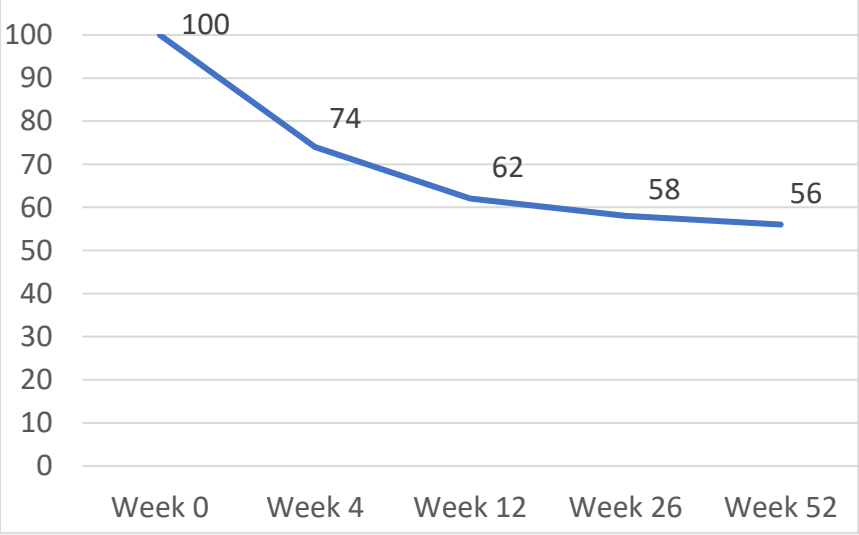
The table (table 3) below highlights our results against our predefined criteria with the green areas highlighting a positive outcome, red a negative and amber an acceptable outcome but not quite reaching the target.

OUTCOME MEASURE	**TARGET**	**RESULT**
GP Practice participation	95%	93%
Recruitment rate for eligible invitees	>50%	23% (invited) 30% (after exclusions 1st visit)
Health professionals signed up to undertake the study receiving training	80%	0%
Participants completing study on LABA/LAMA	80%	56% (37/66)
Follow up data for primary outcome	60%	89%
Completed questionnaires at 12 months	60%	86%
Exacerbation rate, increase from baseline	≤20%	+33%
Quality of life no worse than baseline	>49%	CAT = 42% (28/66) EQ5D = 44% (29/66) Both = 24% (16/66)
Economic data questionnaire return	>50%	86%
12-month inhaler cost equal or better than baseline	=/< baseline cost	YES Mean reduction per patient per year: £279.36

6.72 Number maintained on LABA/LAMA

56% (n=37/66) of the study participants completed the study remaining on the LABA/LAMA therapy (see Figure 21).

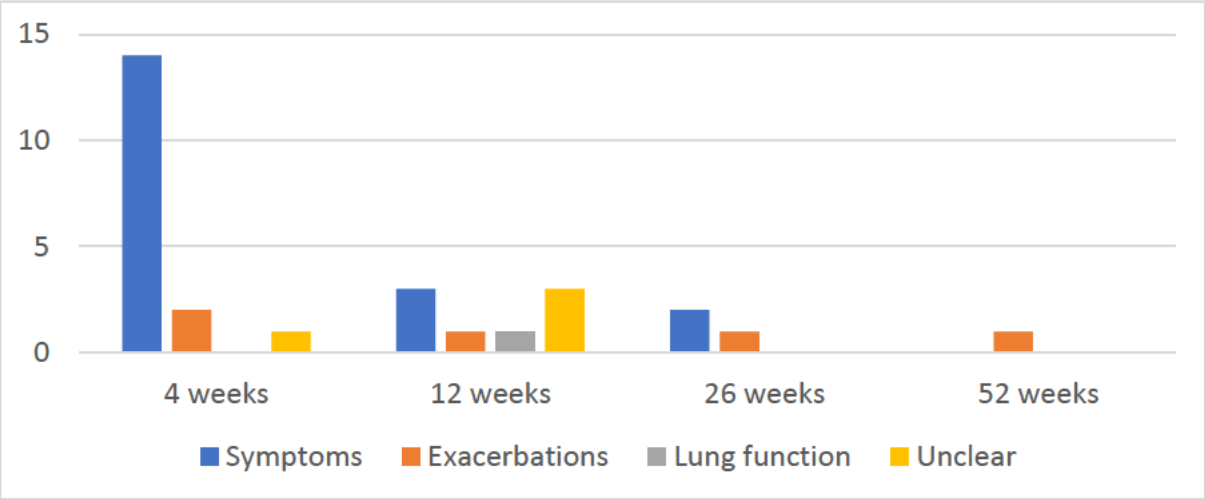
Figure 21**:** Percentage of participants who remained on LABA/LAMA during the study



Most of the group who did restart their ICS did so early into the study, 59% of those who restarted ICS (n=17/29) did so within the first 4 weeks and 86% (n=25/29) had restarted ICS by week 12 out of 52 weeks.

The majority, 66% (n=19), of participants reported wanting to restart their ICS due to an increase in symptoms (mainly breathlessness) with only 17% (n=5) reporting restarting due to an exacerbation. One patient was restarted ICS due to a reduction in lung function and it was unclear in 14% (n=4) why their ICS was restarted (see figure 22).

Figure 22: Reason given for restarting ICS during the study (n=29)



The following tables summarise the main outcome measures and will be discussed further within the text.

Table 4: Outcomes at baseline/12 months prior to study and during/end of study period

Outcomes (mean unless otherwise stated)	12 months prior to study (=63)	Within/end of study (n=60)	p value
Exacerbation rate (median)	1.0	1.0	0.229
Respiratory hospital admissions	0.05	0.2	0.007
FEV1 % predicted*	48.7	48.6	0.883
CAT score*	22.6	23	0.662
EQ-5D VAS*	54.4	54.3	0.913
SABA collection	6.9	7.4	0.188
Adherence (% prescription pick up)	86	97.5	<0.001

*baseline and within study, not 12 months prior to study

Table 5: Outcomes by groups who either maintained on LABA/LAMA or restarting ICS

Outcomes (mean unless otherwise stated)	12 months prior to study	Within/ end study period	P value	12 months prior to study	Within/ end study period	p value
	Maintained LABA/LAMA			Restarted ICS/triple therapy		
Exacerbation rate (median)	1.03	1.19	0.836	2.39	3.52	0.187
Respiratory hospital admissions	0	0.05	ns	0.09	0.43	0.008
FEV1 % predicted*	52.9	53.9	0.38	44.6	42.4	0.04
CAT score*	22.4	22.1	0.817	23	24.6	0.145
EQ-5D VAS*	52	56.2	0.089	58	56.7	0.165
SABA collection	6.14	6.46	ns	8.17	8.87	ns
Adherence % (prescription pick up)	83.4	97.4	<0.001	90.2	99.6	0.032

*baseline and within study, not 12 months prior to study

6.73 Exacerbations during the study (safety)

The distribution of exacerbations amongst participants was significantly non-normal (Kolmorogov Smirnov P<0.03).

There was no change in the median number of 1 exacerbation per patient in the year of the study compared with the year prior (Wilcoxon-rank, p=0.229).

There was a mean increase of 0.52 moderate to severe exacerbations per patient per year, within the whole study group (via intention to treat analysis) during the study when compared to the previous 12 months, see table 6). This is for illustration purposes. Paired t-tests were not applied as the data is non-parametric.

The proportion of the group having less than 2 exacerbations per year reduced from 60% (n=38) in the year prior to 55% (n=33) during the study year (p=n.s).

Table 6: Number of moderate to severe exacerbations treated with steroids or antibiotics in 12 months prior to study and during study period. Data are expressed both as Mean and Medians.

	Number patients having exacerbations	Mean	Standard deviation	Median	Minimum/ Per patient	Maximum Per patient	Number of exacerbations
Exacerbations 12 months prior to study	63	1.56	1.98	1.0	0	10	98
Exacerbations during study	60	2.08	2.72	1.0	0	15	125
p-value	-	N/A	-	0.229	-	-	-

Table 5 describes groups according to whether they were maintained on LABA/LAMA versus those who restarted ICS during the study period:

There was no significant difference in the mean number of exacerbations WITHIN these groups in the year before compared to the study year.

Both groups had an increase in exacerbations from the year prior but there was a greater but not statistically significant mean increase of 1.13 exacerbations (p=0.187) in those restarted on ICS compared to 0.16 increase in exacerbations in those maintained on a LABA/LAMA (p=0.836).

Table 7 also highlights the difference in means in the year prior to the study with those restarting their ICS having over double the number of exacerbations (2.39 vs 1.03, p=0.024).

Table 7: Number of moderate to severe exacerbations treated with antibiotics in 12 months prior to study and during study period by outcome of either continuing on LABA/LAMA or restarting ICS

	Mean number exacerbations 12 months prior to study	Mean number exacerbations during study	*p-value**
Maintained on LABA/LAMA	1.03	1.19	0.836
Restarted ICS	2.39	3.52	0.187

*Wilcoxon signed ranks test

In summary, there was a slight trend to increasing exacerbation rates within the whole group but this was not statistically significant. However, when defined by outcome, there was a significant difference between those restarted on ICS with those maintained on LABA/LAMA group going into the study and this significance became greater during the study. The group who restarted an ICS's exacerbation rate went from just over double to nearly triple the exacerbation frequency of the LABA/LAMA group.

We were unable to compare time to first exacerbation due to the discrepancies and likely inaccuracies in the exact exacerbation dates. However, the distribution of the 125 exacerbations over the study did reveal that only 5% (n=6) occurred within the first 4 weeks and 11% (n=14) within the first 12 weeks. By 12 weeks most (86%) of those who restarted their ICS had done so.

6.74 Respiratory Hospital Admissions

Within the whole study group there was a statistically significant increase in the total number of respiratory related hospital admissions in the study period compared to the year preceding from a total of 3 to 12. The mean rate of hospital admission increased from 0.05 to 0.2 per participant per year (Wilcoxon p=0.007).

When defining outcome by either restarting an ICS or continuing on a LABA/LAMA there was no significant difference in annual number of chest related hospital admissions between groups in the year prior to the study (Mann-Whitney p=0.07). However, there was a significant difference during the 12-month study period (p=0.008) with the greater increase of respiratory hospital admissions within the ICS group (table 8).

Table 8: Chest related hospital admissions (per patient) between groups as defined by outcome of restarting ICS or continuing on LABA/LAMA

	n	12 months prior to study	12 months of study
Finished on LABA/LAMA	37	0	0.05
Finished restarting ICS	23	0.09	0.43
*P-value**	-	0.07	0.008

*Mann-Whitney Test

These respiratory admissions occurred in three individuals in the pre-study period and 9 individuals within the study observation period. Of these 9, two had had an admission in the previous year but 7 had their first admission during the study period.

7 of the 9 (78%) admissions completed the study on an ICS and 4 of these 7 had their ICS restarted within 4 weeks.

6.75 Adverse events

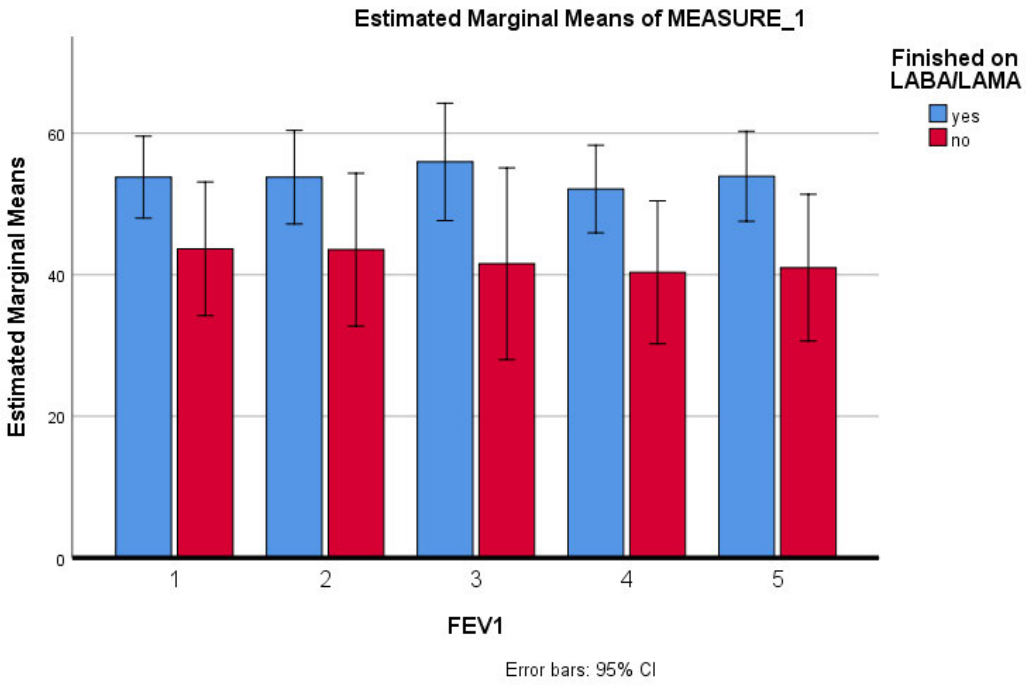
3 participants died within the 12 months study period. All deaths were deemed not related to the study or exacerbations of COPD: one patient had an out-of-hospital sudden cardiac arrest (deemed cardiac), one patient died from a newly diagnosed brain tumour and the last of *cor pulmonale* (had been stable on LTOT for 10 years). A fourth patient died within 4 weeks of completing the study, following post operative complications from an abdominal aortic aneurysm repair.

6.76 Lung Function

The whole group had a mean FEV_1 48.7% at baseline and this did not change significantly at 12 months (mean change of -0.12%, paired sample t-test SD 5.81, CI -1.55 – 1.79, p=0.883).

Figure 23 shows the FEV_1 over the 5 timepoints of the study for those maintained on LABA/LAMA and those who restarted an ICS.

Figure 23: Mean FEV1 % predicted by group (maintained LABA/LAMA or restarted ICS) at: 0, 4, 12, 26 & 52 weeks



There was no change in mean FEV_1 % within the LABA/LAMA group (+1%, 95%CI for difference -3.3 to +1.3%, p=0.378).

However, there was a statistically significant drop in mean FEV_1 % predicted within the group that restarted their ICS (-2.2%, 95%CI for difference -0.14 to -4.3%, p=0.04) although this change of 2.2% in FEV_1.

In summary, FEV_1 did not change significantly within the whole group over the 12-month study period except in those who restarted their ICS who had a significant fall in FEV_1. Those who maintained on a LABA/LAMA had a non-significant increase in FEV_1.

FEV_1 was significantly lower in the ICS group at baseline and remained significantly different at 12 months.

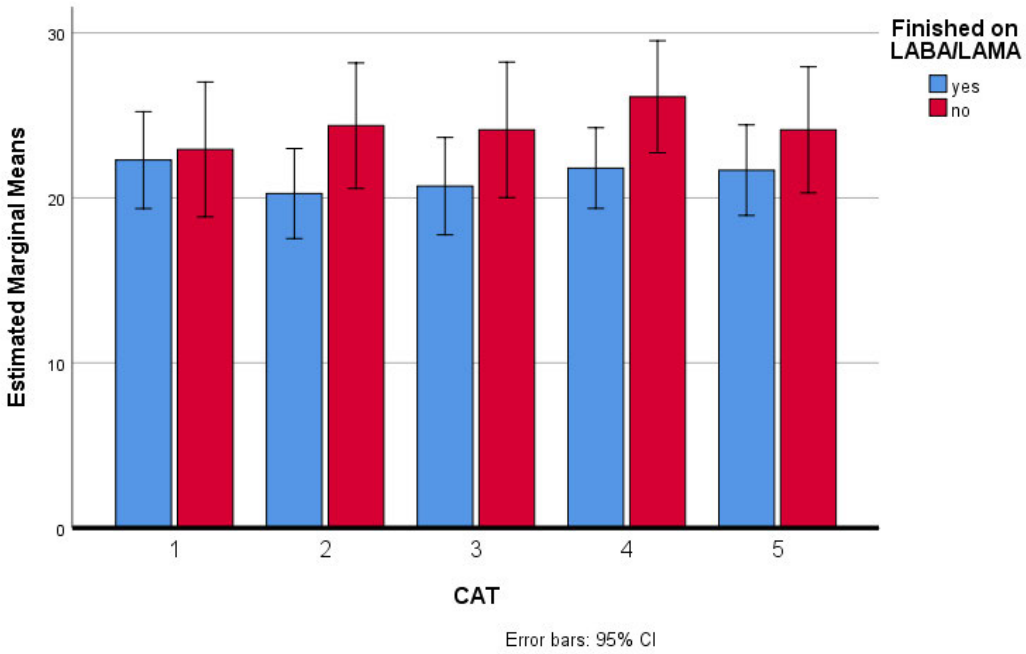
6.77 Quality of Life (CAT & EQ-5D VAS)

The group had a mean CAT score at baseline 22.6 and this did not significantly change at 12 months to 23.0 an increase of 0.4 (95% CI -2.24 to +1.43, p=0.662).

Figure 24 demonstrates that the CAT scores are similar at each of the 5 timepoints of the study. There are minimal but consistent differences in CAT between those who continued on a LABA/LAMA and those who restarted an ICS at baseline over this period. This difference between the LABA/LAMA maintenance versus ICS restarted groups increased through the study with the ICS group having a trend of progressively higher CAT scores and worsening quality of life. These differences between the 2 groups were not statistically significant at baseline (p=0.669) or at 12 months (p=0.244) and do not reach the threshold of clinical importance (difference in CAT score of 2 or more).

Although improved by a mean reduction of 0.3 over the 12 months, the CAT score did not change significantly (p=0.817) in the LABA/LAMA group. Conversely there was a deterioration by a mean increase of 1.6 in the group that restarted their ICS but again this was not significant (p=0.145).

Figure 24: Mean total CAT score by outcome (maintained LABA/LAMA or restarted ICS) at 5 study timepoints: baseline, 4, 12, 26 & 52 weeks



In summary, those maintained on LABA/LAMA there was a mean change in CAT score of -0.3 (95%CI -2.4 to +3.1, p=0.82). This is not statistically significant and below the 2.0 change in score of CAT to be clinically important/noticeable by patients.

In those restarted ICS there was a mean change in CAT score of +1.6 (95%CI -3.7 to +0.6, p=0.15). This is not statistically significant and below the 2.0 change in score of CAT to be clinically important/noticeable by patients.

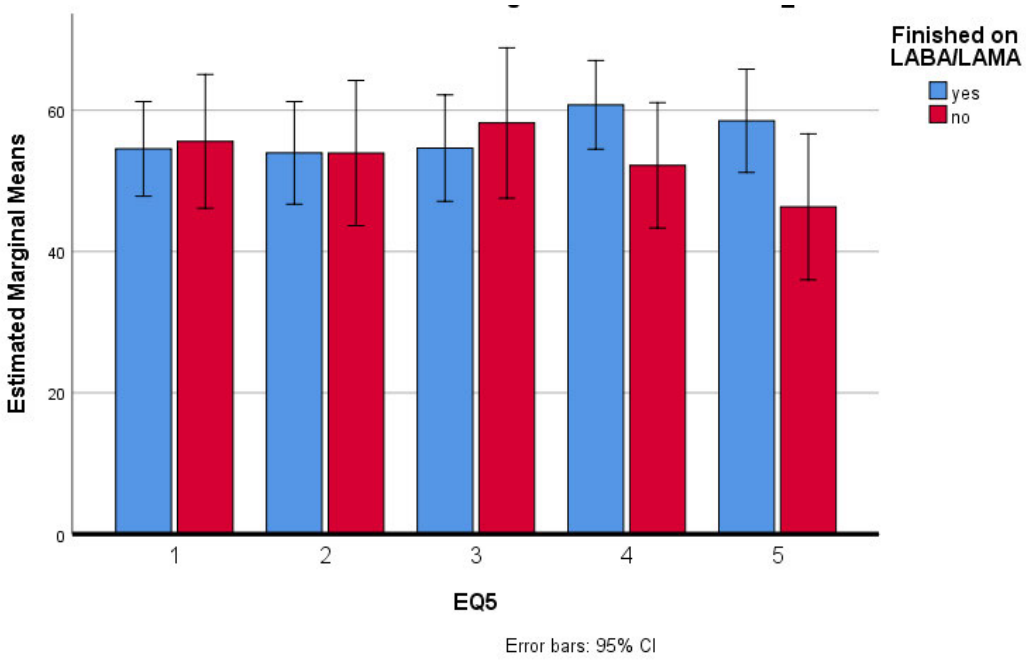
There was no significant difference in CAT score within the whole group at baseline or at 12 months, and no differences between the 2 groups at any timepoints (p=n.s).

In those maintained on LABA/LAMA there was a mean change in EQ-5D visual analogue scale (VAS) of +4.2 (95%CI -9.1 to +6.6, p=0.08). This is not statistically significant. There is no agreed definition of what is a clinically meaningful change in EQ-5D VAS.

In those restarted ICS there was a mean change in EQ-5D VAS of -7.4 (95%CI -3.3 to +18.1, p=0.17). This is not statistically significant and could have occurred by chance.

There was no significant difference in EQ-5D VAS within the whole group at baseline versus 12 months (p=0.91), and no differences between the 2 groups at any timepoints (p=n.s) (figure 25).

Figure 25: Mean EQ-5D VAS score by outcome (maintained LABA/LAMA or restarted ICS) at 5 study timepoints: baseline, 4, 12, 26 & 52 weeks



6.78 Rescue inhaler pick-ups (SABA)

We recorded SABA prescriptions issued in the 12-month preceding and during the 12-month study period as a surrogate marker for SABA use. When measuring the whole group, there was a slight increase in the mean number of SABA prescriptions from 6.9 per patient per year to 7.4 (p=0.188 Wilcoxon signed ranks).

The 0.5 mean increase in SABA issuing rate, half of a typical 200 puff SABA inhaler (100 puffs) would equate to about 50 patient full doses (2 puffs = 1 dose). 50 doses over the year would represent the average participant using one extra puff per week over the study period. This is unlikely to be clinically/pharmacologically important.

In those eventually maintained on LABA/LAMA, they had a mean of 6.14 SABA prescription per patient in the 12 months prior to the study which rose slightly to 6.46 SABA prescriptions per patients in the 12-months of the study (p=n.s).

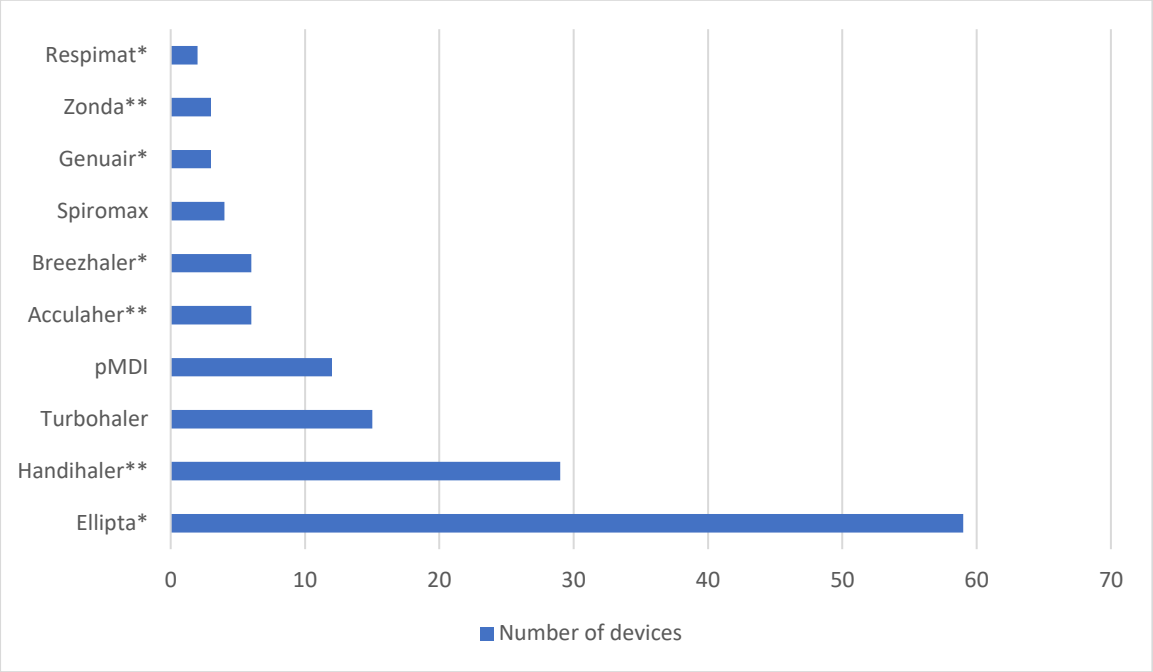
In those eventually restarted on an ICS, they had a mean of 8.17 SABA prescription per patient in the 12 months prior to the study which rose slightly to 8.87 SABA prescriptions per patients in the 12-months of the study (p=n.s).

There was no difference in SABA prescriptions between LABA/LAMA and ICS restarts in the year prior but there was borderline statistical significance (p=0.051, Mann-Whitney) between the groups during the 12 months of the study with the ICS restarts, having around 2.5 SABA inhalers more per patient per year.

6.79 Inhaler Device Choice

Figure 26 highlights that at recruitment the 66 participants were using a combination of 10 different drug delivery devices to administer their preventative inhaled therapies. These were mainly dry powder devices with all having 1, 2 and some using 3 devices to deliver their 3 drugs (ICS, LABA & LAMA); the Ellipta device was the commonest device followed by the Handihaler device.

Figure 26: The number and range of preventive inhaler devices in use at recruitment (baseline)



*Same choice device available

** Similar choice device available (Accuhaler=Ellipta; Handihaler & Zonda = Breezhaler)

61% of participants (n=40) would have had the option of choosing the exact same type of device with the remainder having the choice of one very similar (n=26) to their current one(s). None had to choose a completely different device.

Despite being given the choice and opportunity to try all the placebo devices, the majority 56% (n=37) did in fact choose a new type of device with only 23% choosing the same device (n=15) they were already on and only 21 % choosing a similar (See figure 27) device (n=14). Of those who chose a new device, none recalled having ever used that device before.

Only 50% participants who were already using a pMDI as their preventer chose this device with the exact same number switching to a DPI or Respimat.

No data was collected on the different SABA devices.

Figure 27: The number and range of inhaler devices chosen by participants

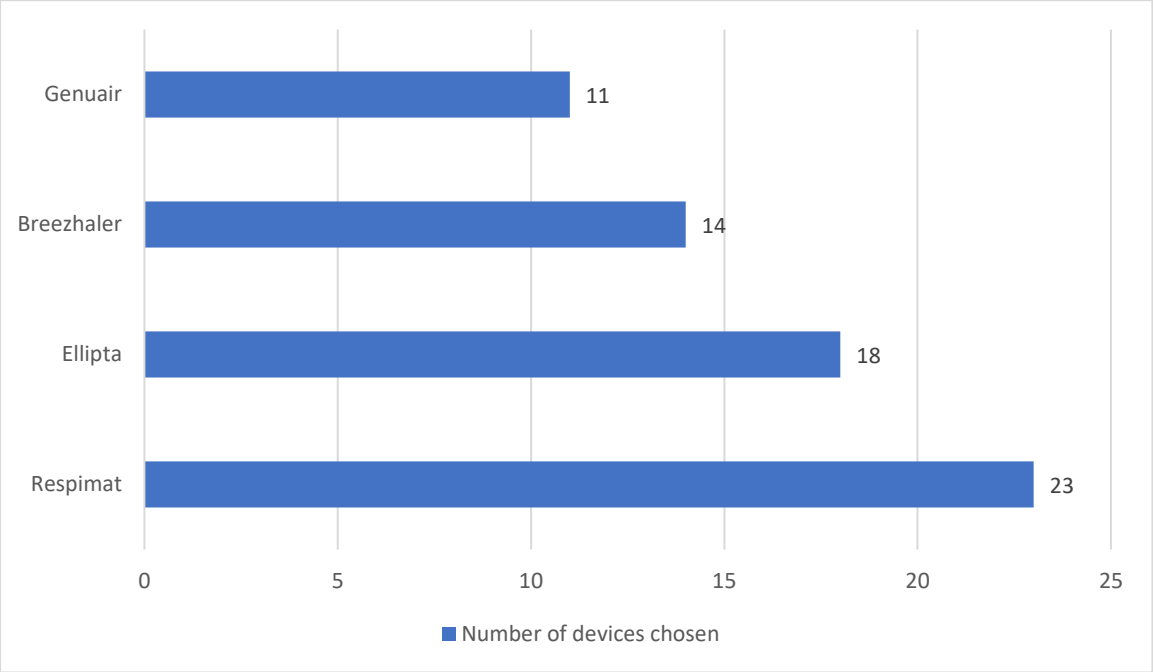


Figure 27 demonstrates that the Respimat device was the most popular choice by this group followed by the Ellipta. Only one participant was unable to demonstrate an adequate inhaler technique with their first-choice device and had to opt for their second-choice device. Of the 37 who completed the 12 months on a LABA/LAMA, 31 (84%) remained on the same device with the other 6 switching to an alternative LABA/LAMA device.

Participants were asked why they chose a particular device. Multiple reasons were given (see table 9).

33 patients preferred once daily dosing and 3 patients preferred the twice daily regime. Being easy to use seemed an important consideration (listed by n=25), being preloaded (n=17) and familiarity using the device or similar before (n=23) were also frequent answers. Maybe less predictable choices were due to aesthetics with n=10 identifying shape and size as being important. Sensory reassurance of dose delivery through sound and sight were also important to a minority (n=10).

Table 9: Reason given for inhaler device choice (patients could list more than one reason)

Reason for inhaler device choice	Number of participants
Once daily dosing	33
Easy to use	25
Preloaded	17
Used device before	17
Vapour not powder	12
Size	7
Used similar before	6
Hear when activated	6
Check dose delivered	4
Dose counter	3
Twice daily dosing	3
Shape	3
No reason	3
Other	5

6.8 Inhaler adherence

Inhaler adherence was calculated as a percentage of the number of inhaler prescriptions issued compared to the number of issues required to be taking their treatment every day i.e., if 12 preventer inhalers were issued and collected over the year then this was considered 100% adherence for one device. If two devices should have been collected per month then 24 issues would be required for 100% adherence. This prescription issuing data was captured on the patient's electronic GP record.

Overall, the group already had a high adherence rate on entering the study (86.0± 20.3%), but this significantly improved whilst in the study, when switching from multiple to a single inhaler to 97.5± 6.8% (p=<0.001).

If we define 80% adherence as a minimum threshold for 'good adherence', then 73% of patients achieved this in the year prior to the study, increasing to 95% patients during the study (p=<0.001).

There was no difference in adherence rates between those maintained on LABA/LAMA or restarting an ICS over the year of the study (see table 10)

Table 10: Adherence rates by outcome 12 months before the study and 12 months of the study (n=59)

	Adherence before % (SD)	Adherence during % (SD)	*p value**
Finished on LABA/LAMA	83.4 (21.4)	97.4 (6.8)	<0.001
Finished on ICS/LABA/LAMA	90.2 (18.0)	97.6 (7.1)	0.032

* Wilcoxon signed ranks

Adherence rates between groups were not significantly different entering the study or during the study (table 11 below).

Table 11: Mean % adherence between groups as defined by outcome of restarting ICS or continuing on LABA/LAMA

	n	12 months prior to study	12 months of study
Finished on LABA/LAMA	37	83.4	97.4
Finished restarting ICS	22	90.2	97.6
P-value	-	0.144	0.822

*Mann-Whitney

6.81 Cost analysis

The cost analysis was calculated using the published NHS inhaler prices in 2016 as described in section 4.14 (206). The mean costs were compared as there would be a natural overall reduction, due to deaths and withdrawals during study. Mean baseline costs were compared to mean inhaler costs at 12 months (see table 12)

Cost of the research team time was not analysed. Discussion within the team concluded that a typical first visit took between 30 and 45 minutes and included explanation and discussion about the study, screening, before consent was gained.

Table 12: Mean cost comparison at baseline and on study completion

Mean baseline cost/patient/month baseline	£63.71	SD ± 13.6
Mean monthly cost/patient/month end of study	£40.43	SD ± 12.1
Potential saving/patient/month	£23.28	P value* =<0.001

* Wilcoxon Signed rank

Based on the above calculations, this would represent an average saving of 12x £23.28 =£279.36 per participant per year, with a total potential saving of £18,437.76 for the entire 66 patients.

The actual saving would have been greater as the figures are based on the final inhaler cost which would not account for the reduced cost of the LABA/LAMA devices collected at the beginning and for each month during the study. An attempt was made to adjust for this, but it was not always clear at which exact month patients switched back from their chosen LABA/LAMA to the triple therapy. There is also a real possibility that some patients had a prescription for both LABA/LAMA and LABA/LAMA/ICS within the same month as they switched back, due to delays in pharmacies stopping medications as new ones are issued. This would increase the overall annual costs for that group but likely to become stable after 1 year as very few switched back to ICS after 6 months.

6.82 Predictors of successful switching

We attempted to identify baseline characteristics that were associated / could predict which patients were most likely to maintain the LABA/LAMA only combination over the 12 months.

We applied the 8 step logistic regression process as described by Hosmer and Lemeshow.(233)

1. Univariate analysis: we first compared variables we thought would be of interest, between those patients with COPD that were maintained on LABA/LAMA versus those that restarted ICS over the following 12 months (table 13)

Table 13: Univariate analysis: first compared variables

VARIABLES	p
Gender	0.383
Age	0.411
Current smoker	0.749
Pack years	0.592
FEV_1 baseline <50%/≥50% predicted	0.009
Lives alone	0.020
Hospital admissions (chest)*	0.999
Treated exacerbations* <2/≥2	0.035
Eosinophil count (latest) <0.3/≥0.3	0.083
CAT (total) baseline	0.613
eMRC baseline	0.740
EQ5D VAS baseline	0.339
SABA use*[#]	0.125
% adherence*[#] <80%/≥80%	0.225
*In 12 months prior to enrolment [#] Prescriptions issued by GP	

2. We then created the first multivariant analysis model included the 6 strongest predictor variables with likelihood ratio Chi2 <0.25(table 14).

Table 14: First multivariant model

Variables in the Equation

		B	S.E.	Wald	Df	Sig.	Exp(B)
Step 1[a]	Pre FEV1 %(1)	-1.871	.721	6.733	1	.009	.154
	lives alone(1)	2.033	.901	5.086	1	.024	7.634
	Pre exacerbations(1)	-1.535	.748	4.207	1	.040	.215
	Last eos count <0.3(1)	1.552	.966	2.583	1	.108	4.721
	SABA 12 months prior	-.125	.087	2.067	1	.151	.883
	% pre adherence(1)	.295	.870	.115	1	.734	1.344
	Constant	1.130	1.104	1.046	1	.306	3.094

a. Variable(s) entered on step 1: Pre FEV1 %, lives alone, Pre exacerbations, Last eos count <0.3, SABA 12 months prior, % pre adherence.

3. We removed all the non-significant variables (p>0.05), refitted the model and tested this reduced model against the previous one using the partial likelihood ratio test. We removed one variable at a time, starting with least significant and removing any that did not reach significance at any point from the model (table 15).

Table 15: Significant variables within the Model

Variables in the Equation

		B	S.E.	Wald	Df	Sig.	Exp(B)
Step 1[a]	lives alone(1)	-1.674	.774	4.680	1	.031	.188
	Pre exacerbations(1)	-1.646	.692	5.661	1	.017	.193
	Pre FEV1 %(1)	1.894	.706	7.196	1	.007	6.649
	Constant	.739	.484	2.331	1	.127	2.093

a. Variable(s) entered on step 1: lives alone, Pre exacerbations, Pre FEV1 %.

4. We checked for undue effects of recently excluded variables by calculating the change in beta between the two models in step 2: A 20% or greater change would indicate that one or more of the excluded variables were important in adjusting the effect of the retained variables (table 16).

Table 16: Checking for effects of originally excluded variables

Variable	% change in B (beta)
Lives alone	17.6
Pre exacerbations	7.2
Pre FEV_1	1.2

5. Checking assumptions in what is (almost) now the final model

All the variables were then reintroduced to the Model one at a time and tested to ensure none became significant. If Wald p-value did not become significant, they were removed immediately. None became significant so there was no change to the Model.

It is important to check any continuous variables for linearity. The 3 variables in the Model are ordinal and nominal. Therefore, there were no continuous variables to check linearity.

6. Interactions

Even though there was no obvious interaction between the 3 variables it could be argued that 'living alone' may be associated with more 'exacerbations' due to e.g. more anxiety living at home. Also, more 'exacerbations' could be associated with a lower FEV_1 at baseline due to recurrent lung damage. Therefore, they would not be independent of each other.

As a result, each variable was tested for co-linearity. Each variable was added to the remaining 2 and their effect tested using the partial likelihood test. All variables remained statistically significant within the Model and the effect using the partial likelihood test did not reach significance (p=>0.26). Therefore, there were no interactions / no co-linearity.

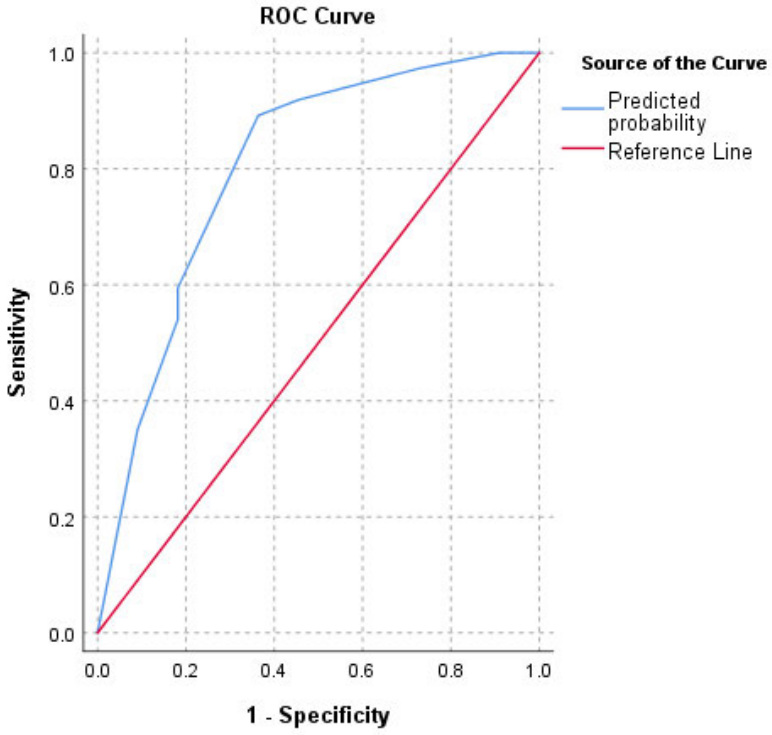
7. Checking model adequacy and fit
    - Goodness of fit

Hosmer & Lemeshow test p=0.783 (p>0.05 suggests at least adequate fit)

Ideally all the expected frequencies should be above 1 and not many of them should be below 5. We had one variable <1, six variables were <5). Therefore, we calculated for each pair of observed & expected variable, using [abs(obs-exp)]/sqrt(exp) and none of them were over 2 so we were reassured that the model is a reasonable fit (see appendix 8).

The ROC curve was then plotted to obtain the area under the curve (figure 28)

Figure 28: Classification accuracy of our 3 variable model for predicting maintenance on LABA/LAMA:



Area under the ROC Curve **for accurately predicting maintenance on LABA/LAMA = 0.802**

The value of 0.802 does support the 3 variables (higher FEV_1, less prior exacerbations and living alone) being an accurate discriminator between the other outcomes measures in predicting those patients who maintained on a LABA/LAMA.

CHAPTER 7: DISCUSSION

The primary aim of the study was to determine if a larger scale study would be feasible. There was certainly appetite from our local Primary Care Practices to support the study and this support would be essential as most of the COPD population are being managed in Primary Care and not via hospital clinics.

Unfortunately, they could not provide any clinical or administrative support to identify potential patients or staff who could be trained to carry out the step-down intervention due to a lack of capacity.

Despite uptake being lower (30%) than our aimed target (>50%), the screening did reveal a large number of patients who may have been eligible and based on study results and current evidence may not require ICS therapy. It is likely we would have had more uptake if study reviews were done closer to home or in their GP surgery rather than on hospital premises with the associated travel and parking difficulties. Reducing the number of study visits earlier may also have improved uptake.

Another important observation during screening was the large number of patients on an ICS/LABA or single long-acting bronchodilators (LAMA). Neither are now recommended and at the time of the study there was still potential and alternatives to maximise therapy to a triple inhaler or at least dual long acting LABA/LAMA.(12)

Having COPD and being initiated on an ICS/LABA may be associated with an overuse of ICS where a dual LABA/LAMA was an option then and recommendation now first line even for exacerbators. (12, 234)

The study did not reveal any safety issues with the outcomes; those maintained on their LABA/LAMA inhaler reported positive gains in terms of symptoms reported by quality of life, had stable or improved lung function, no difference in quality of life and no increase in exacerbations.

The other important aspect of safety which we could not record was the potential for reduced side effects (oral candidiasis, skin thinning and bruising, osteoporosis and pneumonia risk) from participants stopping their daily ICS therapy. Long term reductions in these are important.

The protocol was amended after 8 months as interim analysis revealed that any increase in symptoms and restarting of ICS therapy happened to a patient early in the study with the 12 and 26 week visit offering no additional information. It was hoped that less visits would make the study more attractive but also more likely to reflect real world clinical practice where a change in treatment may initiate an early follow-up but if at that point all was satisfactory, patients may not be routinely reviewed for 12 months.

For the 37 participants who were successfully maintained on a single LABA/LAMA inhaler, the study demonstrated the potential for costs savings over the year of nearly £18.5K. Replicating the study in 2023 would not offer the same cost savings with the introduction of cheaper SITT but these inhalers still cost more than their dual LABA/LAMA alternatives. Certainly, in my practice I still see many patients who still have multiple drugs in multiple devices. Any cost saving in a system under pressure and that has restricted finances, could be redirected for prevention and stopping or limiting the impact of COPD e.g., smoking cessation or pulmonary rehabilitation.

A positive outcome was the 56% (n=37) who were maintained on their LABA/LAMA at the end of the study. With a disease where traditionally, time is no friend and patients experience a gradual slow deterioration, this group, demonstrated a 1% improvement in % predicted FEV_1, 0.3 point improvement in CAT and 4.2 point improvement in EQ-5D VAS – certainly no deterioration. There were very small but statistically non-significant increases in exacerbations, hospital admissions which could then account for the small, non-significant increase in SABA use. Of course, a significant limitation with our statistical results being the study was a feasibility study and not powered for statistical outcomes.

Predictably, in a non-randomised study there were baseline differences in those who eventually restarted an ICS from those who maintained on a LABA/LAMA for the full 12 months. Those restarting ICS had double the number of exacerbations in the year before the study, slightly worse lung function, worse CAT and EQ-5D VAS scores and higher SABA use at baseline. Those maintaining on a LABA/LAMA maintained many of these outcomes, the patients in the ICS restart group deteriorated and the gap at times increasing between groups.

Could stopping the ICS even briefly have accelerated their decline? This is unlikely as most of the participants restarted their ICS within 4 weeks of starting the study and the published benefits in terms of exacerbation reductions are small and over longer periods.

Interestingly, only 17% of ICS-restarts reported having to restart their ICS secondary to an exacerbation and only 11% of exacerbations occurred within the first 12 weeks by which point 86% of restarters had already gone back onto their ICS. Most of the patients who had a hospital admission had already restarted their ICS at 4 weeks, and prior to any admission. We are confident that those with a background of asthma or atopy were excluded. There were no differences in potential asthma traits (age, smoking history, eosinophil counts) between those restarting ICS versus those continuing LABA/LAMA. Undiagnosed asthma is unlikely to have been the cause of the increased symptoms reported by 66% restarters as being the reason for restarting their ICS.

Being an open non-blinded study, participants were aware they were taking 1 less drug and this could drive anxiety. However, despite exacerbations being the main indication within current guidelines for initiating an ICS, we know from blinded placebo-controlled studies initiating an ICS can have a positive impact on lung function and quality of life including symptoms.(181, 185)

Our Model identified 3 variables that together predicted maintaining on a LABA/LAMA during the study period: FEV_1>50% predicted, <2 exacerbations in the 12 months prior to enrolment or cohabited. The link between disease progression, decline in lung function and exacerbations seems a logical one. Current guidelines and reports identify exacerbations as the key indicator for initiating an ICS (not as monotherapy but in combination) and an intervention to reduce this risk.(12, 68, 130) Blood eosinophil counts did not have any predictive value in determining who was able to maintain on a LABA/LAMA despite being beneficial in identifying those exacerbators who would benefit from an ICS.(235) This may be due to the high numbers of participants who had no exacerbations within the preceding year or simply the study having insufficient number and power to see any predictive value or in line with the FLAME results, eosinophil counts did not seem to impact on exacerbations (226)

Adherence rates within the study were significantly higher than typically reported in the literature but we have to accept we could only use prescriptions issued as a surrogate marker of adherence. Despite very good adherence rates within the group, we did see a further significant increase in adherence over the study period compared to the preceding year. There are several plausible explanations: It’s plausible that a reduction in the overall numbers of inhalers and a greater number going onto once daily dosing, would simplify understanding

and commitment. (204) Could giving them the choice of device improve their satisfaction rates and thus make them happier to take more regularly? (78, 81) Could it have just been related to being in a research study and having a greater number of reviews within the 12 months?(83) By agreeing to participate in a research study it could reflect a more motivated COPD population and that they knew they were being researched so might alter behaviour (the Hawthorne effect). Participants were not specifically told adherence rates was one of the outcomes being measured. With adherence to medication strongly related to better clinical outcomes, these are important questions that warrant further study.

Could device choice and adherence be important and previous inhaler exposure be an influence on selection? The Respimat device was the only non-dry powder LABA/LAMA inhaler device and the reason it was chosen most frequently from a very low baseline could be that patient's previous use of pressurised metered dose inhaler (pMDI) aerosol devices with the Respimat arguably the closest device to a pMDI. Despite extensive work on reducing the carbon footprint of inhalers by reducing pMDI prescribing, the Welsh Analytical Prescribing Support Unit shows very slow progress here with pMDIs still being by far the commonest inhaler devices prescribed. An argument against the pMDI influencing selection was only 50% using these as preventers entering the study selected the Respimat device.

The reasons why patients chose different devices are interesting and relevant to practice if we accept the link between satisfaction, adherence and clinical outcomes. The once daily dosing was clearly the main reason given by patients for choosing a particular device. However, a much smaller number (8%) preferred a twice daily inhaler - possibly because they get significant night-time symptoms as their once daily morning inhaler wears off or they perceive it to? If we do not give real choice and work with our patients, then we run the risk of them being dissatisfied with poor adherence and poor clinical outcomes. This could be an important point if organisations consider restricting formularies to a small number of devices or individual clinicians fail to get familiar with the options available and choose from a narrow range.

Adherence and choice are important factors in chronic disease management and 'working with patients' is the first of the 4 Prudent Healthcare Principles adopted systematically by Welsh Government:

1. Achieve health and wellbeing with the public, patients and professionals as equal partners through co-production

2. Care for those with the greatest health need first, making most effective use of all skills and resources

3. Do only what is needed – no more, no less – and do no harm

4. Reduce inappropriate variation using evidence-based practices consistently and transparently

Co-production is where health professionals work with the public and patients, treating them as equals not using an Activity-Passivity Model but one of mutual participation. Four elements are needed: good 2-way communication, empathy, trust and maintaining professional boundaries. (6) In the study they could choose their own device rather than been recommended one and knew they could revert back to their original treatment or chose another device. The choice and control they had may have improved their satisfaction and in turn adherence.

The second principle of caring for those with the greatest need first, helps a healthcare system with limited resources and unlimited need start to ration. The burden of COPD on patients and the NHS is significant (See Chapter 1). This intervention looks safe and feasible with clinical improvements and cost savings.

The third principle 'Do only what is needed – no more, no less – and do no harm'. In the context of this study, a reduction in overall drug usage whilst achieving equivalent or better outcomes and no harm is strongly aligned. We stopped likely unnecessary treatment is a significant proportion of people, reducing the steroid burden and potential side effects.

The fourth principle, 'Reduce inappropriate variation using evidence-based practices consistently and transparently'. This study as a feasibility study generates new evidence that one day could be adopted at scale and give clinicians the confidence to reduce ICS/unnecessary drugs and this process could be scaled to reduce inappropriate variations in care. Updated guidelines are already recommending target ICs therapy in certain patient groups. (236)

Being a real-world study allowed recruitment from a typical COPD population without many of the exclusion criteria (especially co-morbidities and concomitant medications) that can often restrict pharma-sponsored study entry. We collected a variety of outcome measures from clinical, physiological to patient reported quality of life measures. With a broad population and the variety of outcomes measures the results are more likely of reflect

outcomes that would be reproduced in a typical clinical setting and not only relevant for a small sub-set of COPD patients attending specialist research centres. (4) This makes the results more generalizable and valid to everyday clinical practice. The outcome measure used (lung function and CAT) are readily available and widely used. Routine data is already held (exacerbations and issuing of prescriptions) along with the frequency of visits would allow the protocol to be implemented and monitored within a clinical setting without extra resources, another strength of the study.

Being open label, it does increase the risk of bias by researchers, participants and clinicians. Not being randomised or having a placebo /control group precludes us from determining any cause or effect from any intervention, but it does identify associations. Being a small study will have reduced its power to identify potential important outcomes that may come to light with larger numbers. It does however give a basis for a future study and support power calculations to inform any study design.

CHAPTER 8: CONCLUSIONS AND THE WAY FORWARD

The study is consistent with larger randomised controlled trails in that it identifies there are patients who have COPD who are prescribed an ICS that could be safely stopped in a single visit. Exacerbations, particularly recent exacerbations seem to be a key factor in predicting those patients who can safely stop with the severity of airflow obstruction being another consideration. Identifying and stopping an ICS has potential to reduce long term side effects and save money which could be redirected to other services.

Based on the predefined ACCEPT criteria our protocols were safe and adequate data collection possible which could make a larger study feasible. Recruitment targets would have to be reduced but we have proven the potential population is out in Primary Care and reducing the number of visits earlier and providing the care closer to the patient may have had a bigger impact on recruitment. Transferring the intervention from a specialist respiratory researcher to a primary care practitioner would be a challenge without funding or resources as they do not currently have the capacity to undertake.

However, since the initiation of this study evidence, guidelines and clinical services have moved on to the point that undertaking a larger study would be inappropriate and work should focus on prudent inhaler prescribing being part of everyday clinical practice. There are now international guidelines in place to support clinicians to undertake this work in a safe structured way. (236) These stratify the risk and appropriateness of stopping an ICS by exacerbation rate and eosinophil count. They conclude an exacerbation rate of <2/yr with no hospital admissions being a point to consider stopping an ICS, especially if the eosinophil count is <300 cells·μL^{-1}. I would also propose that any work on prudent prescribing and stopping an ICS not be done in isolation but combined with other ways to maximise the patient's treatment including ensuring where appropriate, patients are receiving SITT instead of MITT and dual long-acting bronchodilators instead of single. This should be done by working with the patient with equal priority given to other evidence based non-pharmacological treatments such as, smoking cessation, winter vaccinations, pulmonary rehabilitation and weight management/healthy eating.

How this is implemented and by who probably remains the biggest challenge. Changing the prescribing patterns and culture will be challenging and requires education, support and time. Even then there is still the issue of capacity and resources required to implement change. We

have to look at how we can support health professionals make this easier – technology may be helpful in identifying deficits in care e.g. exacerbation frequencies, eosinophils counts, those who have not received key interventions such as smoking cessation and pulmonary rehabilitation. Having this information automatically would allow for easier and quicker optimisation or stepping down of treatments. Focusing interventions on the higher risk may improve results for that individual and our populations as a whole.

This study and the proposals above fit very well with the 4 principles of Prudent Healthcare outlined in chapter 1. (1, 2) Health professionals working in partnership with patients and maximising appropriate evidence-based interventions will result in improved health and well-being in this population. COPD is a prevalent condition with a heavy burden which is incurable and patients have many unmet needs, high mortality which is still rising in contrast to other chronic conditions (e.g., cardiovascular disease).

Maximising current pharmacological treatments is just one way of impacting on the disease. It needs to fit with prevention, improved case finding, earlier diagnosis, removing causes and increased access to non-pharmacological treatments. Implementing such a truly multi-professional service will reduce unnecessary variations in care and improve the care of this vulnerable population. If we can do this and also reduce risk from unnecessary side effects, reduce waste and save money or redirect finances then we have applied Prudent Care to improve outcomes in COPD.

In terms of future research, more work is clearly required around the area of co-production and its potential impact on adherence. I suspect patients do not always get the option and any say in device choice and if the link with adherence were proven it could result in a significant change to clinical practice which could have significant changes on both individuals' morbidity and quality of life and at the same time reduce the burden on the NHS.

APPENDICIES

Appendix 1: Research Ethics Committee approvals

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

Gwasanaeth Moeseg Ymchwil
Research Ethics Service

Arloesi'r gan Lywodraeth Cymru
Funded by Welsh Government

WALES REC 7
PO Box 108
Building 1
St David's Park
Jobswell Road
Carmarthen
SA31 3WY

Tel: 01267 225045
Email: sue.bond@wales.nhs.uk

Professor Keir Lewis
Respiratory Centre
Hywel Dda University Health Board
Prince Philip Hospital
Llanelli
SA14 8QF

15 February 2017

Dear Professor Lewis

Study title: **sTep dOWn inhAlers in the Real worlD (TOWARD)- a feasibility study of prudent prescribing for Chronic Obstructive Pulmonary Disease**
REC reference: **17/WA/0009**
IRAS project ID: **212862**

Thank you for your email of 14 February 2017, responding to the Committee's request for further information on the above research and submitting revised documentation.

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

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

Confirmation of ethical opinion

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

Conditions of the favourable opinion

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

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

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise). Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

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

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

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

Registration of Clinical Trials

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

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

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

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

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

Ethical review of research sites

NHS sites

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

Non-NHS sites

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

Approved documents

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

Document	Version	Date
Covering letter on headed paper		13 December 2016
GP letter	3	14 February 2017
IRAS Checklist XML [Checklist_16122016]		16 December 2016
Letters of invitation to participant	2	14 February 2017
CAT - validated questionnaire		24 February 2012
Screening checklist	1	27 July 2016
Inhaler checklist	2	16 October 2016
External review		05 October 2016
MHRA Notification that a CTA is not required]		09 February 2017
Participant consent form	3	14 February 2017
Participant information sheet (PIS)	3	14 February 2017
REC Application Form [REC_Form_16122016]		16 December 2016
JSRC letter		08 December 2016
Research protocol or project proposal	5	14 February 2017
Response to Request for Further Information [Email]		14 February 2017
Summary CV for Chief Investigator (CI) Professor Keir Lewis		
Summary CV for student Mr Joe Annandale		
Summary CV for supervisor (student research) Dr Hayley Hutchings		
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Summary protocol TOWARD]	1	13 December 2016
Validated questionnaire [EQ-5D-3L]		13 December 2016

Statement of compliance

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

After ethical review

Reporting requirements

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

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

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

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the

feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

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

17/WA/0009	Please quote this number on all correspondence

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

Yours sincerely

[redacted]

pp. Dr Gareth Davies
Chair

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mr Chris Tattersall*

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

Gwasanaeth Moeseg Ymchwil
Research Ethics Service

Ariennir gan Lywodraeth Cymru
Funded by Welsh Government

Wales REC 7
c/o Public Health Wales
Building 1
Jobswell Road
St David's Park
SA31 3HB

Telephone : 01267 61 1164
E-mail : sue.byng@wales.nhs.uk
Website : www.hra.nhs.uk

Professor Keir Lewis
College of Medicine
University of Swansea
Swansea
SA2 8PP

6 June 2019

Dear Professor Lewis

Study title:	**sTep dOWn inhAlers in the Real worlD (TOWARD)- a feasibility study of prudent prescribing for Chronic Obstructive Pulmonary Disease**
REC reference:	**17/WA/0009**
Amendment number:	**2**
Amendment date:	**07 May 2019**
IRAS project ID:	**212862**

The above amendment was reviewed by the Sub-Committee in correspondence.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Letters of invitation to participant [tracked]	3	07 May 2019
Letters of invitation to participant [clean]	3	07 May 2019
Notice of Substantial Amendment (non-CTIMP)	2	07 May 2019
Research protocol or project proposal [tracked]	7	07 May 2019
Research protocol or project proposal [clean]	7	07 May 2019

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

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

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

17/WA/0009:	**Please quote this number on all correspondence**

Yours sincerely

[redacted]

pp.Dr John Buchan
Chair

E-mail: Wales.REC7@wales.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mr Joseph Annandale*

Appendix 2: Hywel Dda R & D Approval

GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Hywel Dda University Health Board

Research & Development Department
Dr Lisa Seale, Senior R&D Manager – lisa.seale@wales.nhs.uk
Chris Tattersall, R&D Manager – chris.tattersall@wales.nhs.uk
Lisa Jahan, Research Assistant – lisa.jahan3@wales.nhs.uk
Rachel Gemine, Portfolio Coordinator – rachel.e.gemine@wales.nhs.uk

Ref: CT/LJ/Ref: 212862
Date: 17 May 2017

CONTACT: Chris Tattersall
Research & Development Manager
Withybush General Hospital
Fishguard Road
Haverfordwest
Pembrokeshire
SA62 1PZ
Tel: 01437 773813

Ysbyty Cyffredinol Llwynhelyg
Heol Abergwaun, Hwlffordd,
Sir Benfro, SA61 2PZ
Rhif Ffôn: 01437 763813

Professor Keir Lewis
Respiratory Centre
Hywel Dda University Health Board
Prince Philip Hospital
Llanelli
SA14 8QF

Dear Professor Keir Lewis

R&D Ref	212862		
Project Title	sTep dOWn inhAlers in the Real worlD (TOWARD)		
REC Ref	17/WA/0009	**IRAS Ref**	212862
Latest Protocol	5.0	**Protocol Date**	14 February 2017
Site	PPH	**PI**	Joe Annandale

Thank you for submitting your proposal to us for approval for the project to be carried out within this Health Board. Among the documentation considered in support of your application are the following documents, which are currently approved for use:

Document	Version	Dated
Protocol	5	14 February 2017
Research participant information sheet (PIS)	3	14 February 2017
Research Participant Consent Form	3	14 February 2017
Research participant Invitation Letter	2	14 February 2017
GP Information Sheet	3	14 February 2017
REC Approval Letter		15 February 2017

This approval includes all relevant amendments up until the date of this approval letter.

All Research Governance checks have been completed and passed. I have received the comments from the review panel and have not received any objections to the project going ahead. Please accept this letter as approval for the project to proceed in Hywel Dda University Health Board at the sites listed, following study initiation visits if appropriate.

Please endeavour to recruit participants to your estimated time and target and for the first participant to be recruited within 30 days of approval. If there is any assistance you feel we can help with to achieve this, please be in touch.

Under Research Governance, you are required to:

- Ensure that all visiting researchers are in possession of a valid Letter of Access or Honorary Research Contracts for the Health Board.

- Adhere to the protocol approved by the REC and inform the R&D office of any changes (including changes to the end date of the project) and ensure any changes are referred to the Research Ethics Committee(s) or any other regulatory authorities as appropriate.

- Ensure all study personnel adhere to the sponsors Standard Operating Procedures (including Consent, etc). Health Board sponsored SOPs can be found on the Health Board Intranet site or via the R&D office.

- Inform the R&D Office of any relevant adverse/serious adverse events that may occur, whilst also reporting these through the proper channels in the Health Board, and according to the sponsor's protocol and procedures.

- Complete any interim and final reports requested by the R&D Office. If sponsored by this Health Board, you will be asked to present your findings on completion.

- Comply with the Welsh Government Research Governance Framework for Health & Social Care in Wales (2nd Edition 2009) and co-operate with any audit inspection of the project files.

- Ensure that your research complies with regulatory requirements and legislation relating to: Clinical Trials, Data Protection Act 1998, Health & Safety, Caldicott Guidelines, ICH Good Clinical Practice (GCP) and the use of Human Tissue for research purposes, as appropriate for the duration of the study.

- Ensure that all training courses requested by the Sponsor are completed successfully by all relevant members of the research team before any research activity is carried out. All research staff undertaking clinical trials of an investigational medicinal product (CTImps) must be GCP trained, and should continue to update their GCP training every 2 years. Copies of GCP certificates should be filed in the TSF and forwarded to the R&D Department.

- Ensure that all researchers are in receipt of the relevant Personnel/HR documentation in order to conduct research activity in the Health Board, and inform the R&D office of any additional study staff.

In addition:

- It is the local research lead's responsibility to upload recruitment data in all portfolio studies using the following link: http://www.crnoc.nihr.ac.uk/about_us/processes/portfolio/p_recruitment . If you need any support in uploading this data, please contact the Research & Development Department.

- For non-portfolio studies the local research lead should inform the R&D department of their quarterly recruitment figures (or as requested by the department) and the date of first recruited patient.

- To apply for adoption onto the NISCHR CRP, please go to: http://www.wales.nhs.uk/sites3/page.cfm?orgid=580&pid=31979. Once adopted, NISCHR CRP studies may be eligible for additional support through the NISCHR Clinical Research Centre. Further information can be found at: http://www.wales.nhs.uk/sites3/page.cfm?orgid=580&pid=28571 and/or from your NHS R&D

office colleagues.

- Please note that if you wish to extend your project to other sites within the Health Board, or to other Health Boards or NHS bodies you must obtain the approval of all NHS bodies concerned. If the project is sponsored by this Health Board you must notify the R&D Office. Failure to notify may result in suspension or closure of the project.

With all good wishes for the research.

Yours sincerely

Dr Sam Rice
Deputy Director of Research & Development
Hywel Dda University Health Board

Appendix 3: Joint Study Review Committee Approval

GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Abertawe Bro Morgannwg University Health Board

R&D
RESEARCH & DEVELOPMENT

Dyddiad/Date: 8 December 2016

Tel: 01792 530888
Fax: 01792 530887
Email: anne-claire.owen@wales.nhs.uk
abm.rd@wales.nhs.uk

Professor Keir Lewis
Professor in Respiratory Medicine
Swansea University and
Honorary Consultant in Respiratory and General Medicine
Hywel Dda University Health Board

Dear Professor Lewis

Re: Study Title: sTep dOWn inhalers in the reAl woRld (TOWARD)

Thank you for submitting your research protocol to the Joint Study Review Committee (JSRC) for review at the meeting held on 5 October 2016 and a revision that was reviewed at a meeting held on 7 December 2016.

I am pleased to inform you that the study has been approved and the next stage is to submit your JSRC approved protocol for NHS REC review and R&D approval.

As part of the conditions of JSRC approval you will be required to provide 6 monthly progress reports to the Committee. These progress reports will be an opportunity for you to highlight your study development to the Committee and equally highlight any concerns or difficulties which may have arisen in the study, for advice from members.

May I take this opportunity to wish you well with your study.

Yours sincerely

Professor Cathy Thornton
Deputy Chair, Joint Study Review Committee

cc. Joseph Annandale, Respiratory Nurse Specialist, Hywel Dda UHB
Chris Tattersall, R&D Manager, Hywel Dda UHB

Appendix 4: Participant information sheet

PARTICIPANT INFORMATION SHEET – Version 5, 18th December 2018

Title of research study: "sTep dOwn inhalers in the reAl WorlD (TOWARD)**"**
Rec reference: 17/WA/0009

You are being invited to take part in a research study. Before you make a decision it is important to explain why the research is being conducted and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Do not hesitate to ask us if there is anything that is unclear or if you would like additional information. Take time to decide whether or not you wish to take part in our study.

1. What is the purpose of the study?

We believe that some patients may be receiving medicines (steroids) in inhalers that they may not need but do have side effects. It is not known how best to stop inhaled steroids and this is one of the reasons the research is being conducted. New inhalers contain medicines that open the breathing tubes in your lungs and appear to be equally as good or better than your current one containing steroids but with less potential side effects. We want to see if the promising results from trials of these new inhalers done in specialist settings, can have the same benefit in real-life. We want to try you on these new inhalers and at the same time stop your inhaled steroids.
This study is part of an educational PhD qualification and is a pilot study which may lead to a larger study.

2. Why have I been chosen to participate?

Your doctor is treating you for a lung condition called Chronic Obstructive Pulmonary Disease (COPD) with at least two inhalers, one of which includes steroids.

3. Do I have to participate in this study?

It is up to you to decide whether you would like to take part or not. If you decide to take part, you will be given this Participant Information Sheet and we will ask you to sign a Consent form. You are free to withdraw from the study at any time without providing us with a reason. Information regarding your participation up to this point may already be used.

4. What will happen to me if I agree to participate in the research?

Firstly, we will ask you some questions about your health. We will then ask you to do a breathing test known as spirometry (which you should have done before). We will show you the four new inhalers so you can choose which inhaler device you like. We will check you are able to use it properly or find the best one.
After this first assessment there will be 2 more visits to your GP surgery/hospital over the year after approximately 4 and 52 weeks. Here we will ask you to repeat the blowing test and complete 2 short questionnaires to see how you are doing

after we have stopped the inhaled steroid. If you feel worse, we, your GP or nurse prescriber or nurse specialist can always restart your previous inhalers, including the inhaled steroid. This can be done at any time during the study and we would still see you as planned and reassess your condition. Any exacerbations should be reported to the research team at the numbers below or through usual channels. Your GP will be informed of your participation in this study.

5. What will I have to do?

There are no lifestyle restrictions. We will want you to continue your normal activities and all usual health treatments and medications. If you become unwell you should still contact your GP Practice, out-of-hours emergency service or hospital.

6. What are the side effects of participating in this study?

There is a small chance that you may have an increased number of exacerbations when we stop the inhaled steroid but recent research suggests this is unlikely and the new inhalers can be better than ones containing steroids. You will be carefully monitored we will need 5 minutes of your time to answer the screening questions and about 30 minutes to look at which inhalers suits you best. The spirometry (blowing test) is safe and simple and normally recommended every year by your GP anyway.

7. What are the benefits associated with me taking part in this research study?

Taking part will ensure an up-to-date clinical assessment and lung blowing tests and inhaler review. You should end-up on your choice of the most appropriate inhalers for your COPD and reduce the potential risk of side-effects from steroids. Unfortunately, we cannot pay you for participating in this study. No travel expenses would be reimbursed for scheduled visits to primary care whereas they may be available for research visits to hospital sites.

8. What will happen if something goes wrong?

If you feel that you have any reason to complain about any aspect of the way you have been approached in the hospital or further treated during the course of the study, the normal National Health Service complaints mechanisms are available to you.

9. Will my participation in this study be kept confidential?

All the collected information about you during the course of our research programme will be kept strictly confidential. Any information that leaves the hospital or GP Practice will be coded so you cannot be identified from it. In addition, we will not give any identifiable information to life insurance, private medical insurance companies or any other third parties.

10. What will happen with the results generated by this research programme?

The findings from our study may be published in scientific journals and presented at conferences / meetings. No patient individuals can be identified in the reports. You are welcome to contact the researchers for a report after 2 years.

11.Who is organizing and funding this research?
This research is the result of a collaboration between Hywel Dda University Health Board with advice from other lung specialists and pharmacists in Wales and Bristol. Some funding has come from Pfizer Inc. a company that makes inhalers and we have approached 2 other commercial companies for support. No company has influenced the design or conduct of this research and will not have any access to your personal results or how, when or where the study will be published.

12.Who has reviewed the study?
Our research study has undergone review by medical doctors and scientific researchers within Hywel Dda University Health Board and across Wales as well as an NHS Research Ethics Committee (WALES REC 7).

Contacts for further information:
For independent advice, please contact Mr Chris Tattersall, R&D Department, Withybush Hospital, Tel: 01437 773813.
Email: chris.tattersall@wales.nhs.uk

If you have any further queries please do not hesitate to contact:

Prof. Keir Lewis
Chief Investigator
Hon. Consultant, Hywel Dda University Health Board &
Professor of Respiratory Medicine, Swansea University
Telephone: 01554 783133
Email: k.e.lewis@swansea.ac.uk

Mr Joe Annandale
Respiratory Nurse Specialist
Hywel Dda University Health Board
Prince Philip Hospital
Llanelli
Telephone: 01554 783515
Email: joe.a.annandale@wales.nhs.uk

Additional Data Protection information

Study Title: sTep dOwn inhalers in the reAl WorlD (TOWARD)
Chief Investigator: Prof. Keir Lewis
Principal Investigator: Mr Joe Annandale
Study Sponsor: Hywel Dda University Health Board.

Hywel Dda University Health Board is the sponsor for this study based in Wales. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Hywel Dda University Health Board will keep identifiable information about you for 10 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at:
http://www.wales.nhs.uk/sitesplus/862/page/74864

Hywel Dda University Health Board will collect information from you and your medical records] for this research study in accordance with our instructions.

Hywel Dda University Health Board will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the sponsor organisation and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The only people in the sponsor organisation who will have access to information that identifies you will be people who need to contact you to collect information from you or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

Hywel Dda University Health Board will keep identifiable information about you from this study for 10 years after the study has finished.

The sponsor organisation will collect information about you for this research study from our hospital databases. This information will include your name/NHS number/contact details and health information, which is regarded as a special category of information. We will use this information to help us answer our research questions.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities,

NHS organisations or companies involved in health and care research in this country or abroad. Your
information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

Appendix 5: Participant consent form

CONSENT FORM Version 5, 18th December 2018

Participant Identification Number:_____

N.B. Three copies will be made for: (1) patient, (2) researcher, (3) hospital notes (if relevant).

Title of the Research Project: "sTep dOWn inhalers in the reAl woRlD (TOWARD)**"**

REC Reference: 17/WA/0009

Research Team: Prof Keir Lewis, Mr. Joe Annandale

Contact Telephone Number: 01554 783133/ 783515

Read carefully the following statements and initial the adjacent box if you agree.

1.	I confirm that I have read and understood the Information Sheet (Version 4, 17th May 2018) for the above study and have had the opportunity to ask questions.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. If I withdraw, previously collected data can still be used.	
3.	I understand that sections of any of my medical notes may be looked at by: responsible individuals from the research team, regulatory authorities where it is relevant to my taking part in research and the sponsor's representatives in Hywel Dda University Health Board for monitoring the conduct of the study. I give permission for these individuals to have access to my records.	
4.	I agree to fill in the questionnaires at all study visits, including the first visit and after around 4 and 52 weeks	
5.	I agree to do a blowing test at all study visits, including the first visit and after around 4 and 52 weeks	
6.	I understand and agree that a letter is going to be sent to my GP informing about my participation in the study.	
7.	I confirm that I have understood all the above statements and I agree to take part in this research study.	

Name of Patient	**Date:**	**Signature:**
Name of Person taking consent or Researcher	**Date:**	**Signature:**

Appendix 6: GP information sheet

GP INFORMATION SHEET (version 3: 14th February 2017)

Ethics Reference: 17/WA/0009

Title of study: sTep dOWn inhalers in the reAl woRlD (TOWARD)

Your patient has agreed to participate in the above research study that is being organised through Hywel Dda University Health Board and Swansea University.

Name:

Date of birth:

New evidence suggests that regimes containing long-acting beta agonists in conjunction with long acting muscarinic antagonist drugs (LABA/LAMAs) alone appear just as good regimes containing inhaled corticosteroids (ICS), even in severe disease and people with exacerbations. However, these data from specialist randomised controlled trials may not be applicable to everyday life.

This research study involves standard assessment of patients with chronic obstructive pulmonary disease (COPD) and stopping their inhaled steroids in one visit but switching to continuing on -maximal bronchodilators and letting them choose which of the new LABA/LAMA inhalers suits them the most .

Some people will have exacerbations if we continue ICS and some will have exacerbations if we stop ICS. We will reduce risk by not including people with possible asthma (on record or screening questionnaire) or someone discharged from hospital within 6 weeks. In the study, we will monitor the feasibility (uptake) and the number of people successfully maintained on dual bronchodilation only as well as monitoring their lung function, exacerbations, quality of life and total prescription costs over 12 months.

All standard NHS treatments will continue throughout the study, including the option to restart inhaled steroids at any time if you or another health professional felt it was appropriate. Clinical management of the patient will not be compromised in any way.

All information will be kept in the strictest confidence and no individual patients can be identified by anyone other than the study team.

Subjects have provided written informed consent and can withdraw at any time from the study.

Professor Keir E Lewis,
Hon. Consultant Physician, Hywel Dda University Health Board &
Professor of Respiratory Medicine, College of Medicine, Swansea University.

Mr Joe Annandale,
Respiratory Nurse Specialist, Prince Philip Hospital, Hywel Dda University Health Board.

Appendix 7: Screening and data collection tool

RESEARCH PROJECT TITLE:

sTep dOWn inhalers in the reAl woRlD (TOWARD) – feasibility study of prudent prescribing for Chronic Obstructive Pulmonary Disease

REC REFERENCE: 17/WA/0009

PATIENT DATA SHEET

DATE OF BIRTH:				
GENDER:	MALE		FEMALE	
NHS NUMBER:				
GP PRACTICE:				
STUDY ID:				
TRIAL SITE ID:				
DATE OF ENROLMENT:				
	Inhaler pickup immediate		Refer to GP for inhaler pickup	

INCLUSION CRITERIA

	YES	NO
GP diagnosis of COPD (QoF code 45)		
Post bronchodilator FEV_1 <80% predicted and FEV/FVC ratio<70%		
Current or ex-smoker with ≥ 10 pack year smoking history		
Aged 40 - 90 yrs old		
Taking any combination of a LABA / ICS / LAMA		
Must answer YES to all the above		

EXCLUSION CRITERIA

	YES	NO
Unwilling or unable to sign informed consent		
Any previous GP or hospital diagnosis of asthma		
Any features of asthma:		
Large variability of symptoms		
History of atopy (eczema, hayfever, nasal polyps)		
Any previous blood eosinophil count >600 mm^3		
A moderate-severe exacerbation of COPD (antibiotics/oral steroids/needing admission to hospital for > 24 hours) within the last 6 weeks		
Life expectancy less than 1 year		
Must answer No to all the above		

VISIT 1 (WEEK 0)

Date of visit / /

Smoking status Current ☐ Ex-smoker ☐

Smoking history ☐ pack years

Co-morbidities

Cardiac	☐
Musculoskeletal	☐
Pneumonias	☐
Mental	☐
Neuro	☐

LTOT? Yes ☐ No ☐

Home circumstances Lives alone Yes ☐ No ☐ Carers ☐ RH/NH ☐

Spirometry

FVC	____ litres	_____% predicted	
FEV_1	____ litres	_____% predicted	
FEV/FVC ratio		Height (m)	m

mMRC dyspnoea breathlessness score

1	2	3	4	5a	5b

Questionnaires completed CAT ☐ EQ-5D ☐

Medication

SABA	☐	LABA	☐
Carbocisteine	☐	Statin	☐
Theophylline	☐	ACE/ARB	☐
LAMA	☐	ICS	☐
Azithromycin	☐	Diuretic	☐
Long term steroid	☐	Beta blocker	☐

Current inhalers:

Completed by:

Follow up: VISIT…….. (WEEK ……..)

Date of visit	/ /			
Has participant continued on new LABA/LAMA inhaler?	Yes		No	
If no, are they using:	Alternative LABA/LAMA inhaler		ICS/LABA/LAMA inhalers	
Reason given for change and date:				
Technique check completed				
Smoking status	Current		Ex-smoker	

Since Visit 1:

Number of exacerbations requiring oral steroids/antibiotics				
Hospital admissions	Chest			
	Non-chest			
Spirometry	FVC	litres	% predicted	
	FEV_1	litres	% predicted	
	FEV/FVC ratio			

Questionnaires completed	CAT		EQ-5D	
Completed by:				

ONE YEAR VALIDATED OUTCOMES DATA

Date of inhaler pickup	Immediate (insert date of consent)	
	GP prescribed (obtain collection date)	

Continued on same LABA/LAMA?	Yes		No	
Switched LABA/LAMA?	Yes		No	

		1 year pre-study	During study year
Number of exacerbations requiring oral steroids/antibiotics			
Hospital admissions	Chest		
	Non-chest		
Prescriptions	LABA/LAMA		
	LABA		
	LAMA		
	ICS		
	ICS/LABA		
	SABA		
	TOTAL		

Completed by:

Appendix 8: Hosmer & Lemeshow: Goodness of fit test

Contingency Table for Hosmer and Lemeshow Test

		Finished on LABA/LAMA = no		Finished on LABA/LAMA = yes		Total
		Observed	Expected	Observed	Expected	
Step 1	1	6	5.450	1	1.550	7
	2	6	5.700	2	2.300	8
	3	2	1.996	1	1.004	3
	4	4	4.850	11	10.150	15
	5	0	.554	2	1.446	2
	6	2	2.444	7	6.556	9
	7	2	1.006	13	13.994	15

Steps	[abs(obs-exp)]/sqrt(exp)	
	Finished on LABA/LAMA = No	Finished on LABA/LAMA = Yes
1	0.2356	-0.4418
2	0.1257	-0.1978
3	0.0028	-0.0040
4	-0.3860	0.2668
5	-0.7443	0.4607
6	-0.2840	0.1734
7	0.9910	-0.2657

None>2

BIBLIOGRAPHY

1. Bradley PW, A.; Buss, P.; Harry, S,; Laing, H.; Shortland, G.; van Woerden, H.C.; Matthias, J.; Puntoni,S. Achieving Prudent Healthcare in NHS Wales. Wales: NHS Wales; 2014.
2. WelshGovernment. Making Prudent Healthcare Happen. Wales: Public Health Wales; 2014.
3. Commission B. Simply Prudent Healthcare - achieving better care and value for money in Wales - discussion paper. 2013.
4. Halpin DMG, Kerkhof M, Soriano JB, Mikkelsen H, Price DB. Eligibility of real-life patients with COPD for inclusion in trials of inhaled long-acting bronchodilator therapy. Respiratory Research. 2016;17(1):120.
5. Living Well With COPD. What is COPD? [Available from: https://www.livingwellwithcopd.com/en/what-is-copd.html.
6. Service NH. Chronic Obstructive Pulmonary Disease (COPD) United Kingdom: Crown Copyright; 2023 [Available from: https://www.nhs.uk/conditions/chronic-obstructive-pulmonary-disease-copd/causes/.
7. Health and Safety Executive. Work-related Chronic Obstructive Pulmonary Disease (COPD) statistics in Great Britain, 2019 2019, October 30 [Available from: https://www.hse.gov.uk/statistics/causdis/copd.pdf.
8. Murgia N, Gambelunghe A. Occupational COPD—The most under-recognized occupational lung disease? Respirology. 2022;27(6):399-410.
9. Blanc PD, Annesi-Maesano I, Balmes JR, Cummings KJ, Fishwick D, Miedinger D, et al. The Occupational Burden of Nonmalignant Respiratory Diseases. An Official American Thoracic Society and European Respiratory Society Statement. American Journal of Respiratory and Critical Care Medicine. 2019;199(11):1312-34.
10. Health and Safety Executive. Chronic obstructive pulmonary disease (COPD) [Available from: https://www.hse.gov.uk/copd/index.htm.
11. De Matteis S, Jarvis D, Darnton A, Hutchings S, Sadhra S, Fishwick D, et al. The occupations at increased risk of COPD: analysis of lifetime job-histories in the population-based UK Biobank Cohort. European Respiratory Journal. 2019;54(1):1900186.
12. Disease GIfCOL. Glogal Strategy for the diagnosis, management and prevention of COPD (2023). 2023.
13. Saetta M, Finkelstein R, Cosio M. Morphological and cellular basis for airflow limitation in smokers. European Respiratory Journal. 1994;7(8):1505-15.
14. McCloskey SC, Patel BD, Hinchliffe SJ, Reid ED, Wareham NJ, Lomas DA. Siblings of patients with severe chronic obstructive pulmonary disease have a significant risk of airflow obstruction. Am J Respir Crit Care Med. 2001;164(8 Pt 1):1419-24.
15. Stoller JK, Aboussouan LS. Alpha1-antitrypsin deficiency. Lancet. 2005;365(9478):2225-36.
16. Shrine N, Guyatt AL, Erzurumluoglu AM, Jackson VE, Hobbs BD, Melbourne CA, et al. New genetic signals for lung function highlight pathways and chronic obstructive pulmonary disease associations across multiple ancestries. Nature genetics. 2019;51(3):481-93.
17. Doiron D, de Hoogh K, Probst-Hensch N, Fortier I, Cai Y, De Matteis S, et al. Air pollution, lung function and COPD: results from the population-based UK Biobank study. European Respiratory Journal. 2019;54(1):1802140.
18. Sarkar C, Zhang B, Ni M, Kumari S, Bauermeister S, Gallacher J, et al. Environmental correlates of chronic obstructive pulmonary disease in 96 779 participants from the UK Biobank: a cross-sectional, observational study. The Lancet Planetary Health. 2019;3(11):e478-e90.
19. British Lung Foundation. Number of people diagnosed with COPD 2018 [Available from: https://statistics.blf.org.uk/copd.
20. NHS Digital. 2019 [Available from: https://www.gpcontract.co.uk/browse/WAL/19.

21. Ruparel M, Quaife SL, Dickson JL, Horst C, Tisi S, Hall H, et al. Prevalence, Symptom Burden, and Underdiagnosis of Chronic Obstructive Pulmonary Disease in a Lung Cancer Screening Cohort. Annals of the American Thoracic Society. 2020;17(7):869-78.
22. Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, et al. Global and regional estimates of COPD prevalence: Systematic review and meta–analysis. Journal of global health. 2015;5(2).
23. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet. 1997;349(9064):1498-504.
24. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007;370(9589):741-50.
25. Haughney J, Gruffydd-Jones K, Roberts J, Lee AJ, Hardwell A, McGarvey L. The distribution of COPD in UK general practice using the new GOLD classification. Eur Respir J. 2014;43(4):993-1002.
26. Yin P, Jiang CQ, Cheng KK, Lam TH, Lam KH, Miller MR, et al. Passive smoking exposure and risk of COPD among adults in China: the Guangzhou Biobank Cohort Study. Lancet. 2007;370(9589):751-7.
27. Liu S, Zhou Y, Wang X, Wang D, Lu J, Zheng J, et al. Biomass fuels are the probable risk factor for chronic obstructive pulmonary disease in rural South China. Thorax. 2007;62(10):889-97.
28. Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. Lancet. 2007;370(9589):758-64.
29. Molfino NA. Genetics of COPD. Chest. 2004;125(5):1929-40.
30. Wood AM, Stockley RA. Unifying the genetics, co-morbidities and management of COPD. Ther Adv Respir Dis. 2008;2(3):113-7.
31. Health AoSa. COPD and Smoking: An experts guide 2018 [Available from: https://ash.wales/copd-and-smoking-an-experts-guide/.
32. Library HoC. What is Chronic Obstructive Pulmonary Disease and who does it affect? : NHS Digital; 2023 [Available from: https://commonslibrary.parliament.uk/what-is-chronic-obstructive-pulmonary-disease-and-who-does-it-affect/.
33. Ho T, Cusack RP, Chaudhary N, Satia I, Kurmi OP. Under- and over-diagnosis of COPD: a global perspective. Breathe. 2019;15(1):24-35.
34. Excellence NIfHaC. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 2018, December 5.
35. Sylvester KP, Clayton N, Cliff I, Hepple M, Kendrick A, Kirkby J, et al. ARTP statement on pulmonary function testing 2020. BMJ Open Respiratory Research. 2020;7(1):e000575.
36. Burgos FG, J. Spirometry course, : www.sibelmed.com; [Available from: https://slideplayer.com/slide/12238245/.
37. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187(4):347-65.
38. National Collaborating Centre for Chronic Conditions: Chronic Obstructive Pulmonary Disease, National CLinical Guideline on Management of Chronic Obstructive Pulmonay Disease in adults in Primary and Secondary care. Thorax. 2004;59(1):1-232.
39. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance--United States, 1971-2000. Morbidity and mortality weekly report Surveillance summaries. 2002;51(6):1-16.
40. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax. 2005;60(11):925-31.

41. Slenter RH, Sprooten RT, Kotz D, Wesseling G, Wouters EF, Rohde GG. Predictors of 1-year mortality at hospital admission for acute exacerbations of chronic obstructive pulmonary disease. Respiration; international review of thoracic diseases. 2013;85(1):15-26.
42. Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax. 2012;67(11):957-63.
43. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax. 2002;57(10):847-52.
44. Esteban C, Quintana JM, Moraza J, Aburto M, Egurrola M, Espana PP, et al. Impact of hospitalisations for exacerbations of COPD on health-related quality of life. Respir Med. 2009;103(8):1201-8.
45. Cote CG, Dordelly LJ, Celli BR. Impact of COPD exacerbations on patient-centered outcomes. Chest. 2007;131(3):696-704.
46. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007;176(6):532-55.
47. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet. 1997;349(9061):1269-76.
48. Menzin J, Boulanger L, Marton J, Guadagno L, Dastani H, Dirani R, et al. The economic burden of chronic obstructive pulmonary disease (COPD) in a U.S. Medicare population. Respir Med. 2008;102(9):1248-56.
49. Antonelli Incalzi R, Fuso L, De Rosa M, Forastiere F, Rapiti E, Nardecchia B, et al. Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. Eur Respir J. 1997;10(12):2794-800.
50. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.
51. Organisation WH. The top 10 causes of death. World Health Organisation; 2020.
52. Morgan A, Peck D, Buchanan DR, McHardy G. Effect of attitudes and beliefs on exercise tolerance in chronic bronchitis. Br Med J (Clin Res Ed). 1983;286(6360):171-3.
53. Killian KJ, Leblanc P, Martin DH, Summers E, Jones NL, Campbell EJM. Exercise Capacity and Ventilatory, Circulatory, and Symptom Limitation in Patients with Chronic Airflow Limitation. American Review of Respiratory Disease. 1992;146(4):935-40.
54. Soriano JB, Lamprecht B, Ramirez AS, Martinez-Camblor P, Kaiser B, Alfageme I, et al. Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2007 and 2011 staging systems: a pooled analysis of individual patient data. Lancet Respir Med. 2015;3(6):443-50.
55. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(7):581-6.
56. Karloh M, Fleig Mayer A, Maurici R, Pizzichini MMM, Jones PW, Pizzichini E. The COPD Assessment Test: What Do We Know So Far?: A Systematic Review and Meta-Analysis About Clinical Outcomes Prediction and Classification of Patients Into GOLD Stages. Chest. 2016;149(2):413-25.
57. Development of a self-reported Chronic Respiratory Questionnaire (CRQ-SR). Thorax. 2001;56(12):954-9.
58. Guerra B, Haile SR, Lamprecht B, Ramirez AS, Martinez-Camblor P, Kaiser B, et al. Large-scale external validation and comparison of prognostic models: an application to chronic obstructive pulmonary disease. BMC Med. 2018;16(1):33.
59. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999;160(6):1856-61.

60. Soler-Cataluña JJ, Martínez-García MÁ, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax. 2005;60(11):925-31.
61. Rothnie KJ, Müllerová H, Smeeth L, Quint JK. Natural History of Chronic Obstructive Pulmonary Disease Exacerbations in a General Practice–based Population with Chronic Obstructive Pulmonary Disease. American Journal of Respiratory and Critical Care Medicine. 2018;198(4):464-71.
62. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. European Respiratory Journal. 2008;32(4):962-9.
63. Forum of International Respiratory Societies. The global impact of respiratory disease 2017 [Available from: https://www.who.int/gard/publications/The_Global_Impact_of_Respiratory_Disease.pdf.
64. McLean S, Hoogendoorn M, Hoogenveen RT, Feenstra TL, Wild S, Simpson CR, et al. Projecting the COPD population and costs in England and Scotland: 2011 to 2030. Sci Rep. 2016;6:31893.
65. National Institute for Health and Care Excellence. Briefing paper - COPD update. 2015.
66. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J. 2009;33(5):1165-85.
67. Soriano JBea. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015,.
68. Global Initiative for Chronic Obstructive Lung Disease. Glogal Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease (2020 Report) 2022 [Available from: https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf.
69. Wurst KE, St Laurent S, Mullerova H, Davis KJ. Characteristics of patients with COPD newly prescribed a long-acting bronchodilator: a retrospective cohort study. International journal of chronic obstructive pulmonary disease. 2014;9:1021-31.
70. Vetrano DL, Bianchini E, Onder G, Cricelli I, Cricelli C, Bernabei R, et al. Poor adherence to chronic obstructive pulmonary disease medications in primary care: Role of age, disease burden and polypharmacy. Geriatrics & gerontology international. 2017;17(12):2500-6.
71. Humenberger M, Horner A, Labek A, Kaiser B, Frechinger R, Brock C, et al. Adherence to inhaled therapy and its impact on chronic obstructive pulmonary disease (COPD). BMC pulmonary medicine. 2018;18(1):163.
72. Dhamane AD, Schwab P, Hopson S, Moretz C, Annavarapu S, Burslem K, et al. Association between adherence to medications for COPD and medications for other chronic conditions in COPD patients. International journal of chronic obstructive pulmonary disease. 2017;12:115-22.
73. Covvey JR, Mullen AB, Ryan M, Steinke DT, Johnston BF, Wood FT, et al. A comparison of medication adherence/persistence for asthma and chronic obstructive pulmonary disease in the United Kingdom. International journal of clinical practice. 2014;68(10):1200-8.
74. Bogart M, Stanford RH, Laliberte F, Germain G, Wu JW, Duh MS. Medication adherence and persistence in chronic obstructive pulmonary disease patients receiving triple therapy in a USA commercially insured population. International journal of chronic obstructive pulmonary disease. 2019;14:343-52.
75. Agh T, Inotai A, Meszaros A. Factors associated with medication adherence in patients with chronic obstructive pulmonary disease. Respiration; international review of thoracic diseases. 2011;82(4):328-34.
76. Zucchelli A, Vetrano DL, Bianchini E, Lombardo FP, Piraino A, Zibellini M, et al. Adherence to COPD free triple inhaled therapy in the real world: a primary care based study. The Clinical Respiratory Journal. 2020;14(8):732-9.

77. Nishi SPE, Maslonka M, Zhang W, Kuo YF, Sharma G. Pattern and Adherence to Maintenance Medication Use in Medicare Beneficiaries with Chronic Obstructive Pulmonary Disease: 2008-2013. Chronic Obstr Pulm Dis. 2018;5(1):16-26.
78. George M, Bender B. New insights to improve treatment adherence in asthma and COPD. Patient Prefer Adherence. 2019;13:1325-34.
79. Janjua S, Pike KC, Carr R, Coles A, Fortescue R, Batavia M. Interventions to improve adherence to pharmacological therapy for chronic obstructive pulmonary disease (COPD). Cochrane Database of Systematic Reviews. 2021(9).
80. Kayyali R, Gebara SN, Hesso I, Funnell G, Naik M, Mason T, et al. Shared decision making and experiences of patients with long-term conditions: has anything changed? BMC Health Serv Res. 2018;18(1):763.
81. Pages-Puigdemont N, Mangues MA, Masip M, Gabriele G, Fernandez-Maldonado L, Blancafort S, et al. Patients' Perspective of Medication Adherence in Chronic Conditions: A Qualitative Study. Adv Ther. 2016;33(10):1740-54.
82. Chrystyn H, Small M, Milligan G, Higgins V, Gil EG, Estruch J. Impact of patients' satisfaction with their inhalers on treatment compliance and health status in COPD. Respiratory medicine. 2014;108(2):358-65.
83. Amin AN, Ganapathy V, Roughley A, Small M. Confidence in correct inhaler technique and its association with treatment adherence and health status among US patients with chronic obstructive pulmonary disease. Patient preference and adherence. 2017;11:1205-12.
84. McDonald VM, Osadnik CR, Gibson PG. Treatable traits in acute exacerbations of chronic airway diseases. Chronic Respiratory Disease. 2019;16:1479973119867954.
85. (ASH) Aosah. Wales Smoking Statistics 2023 [Available from: https://ash.wales/wales-smoking-statistics/.
86. Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey WC, Buist AS, et al. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. Am J Respir Crit Care Med. 2000;161(2 Pt 1):381-90.
87. Anthonisen NR, Connett JE, Murray RP. Smoking and Lung Function of Lung Health Study Participants after 11 Years. American Journal of Respiratory and Critical Care Medicine. 2002;166(5):675-9.
88. Jiménez-Ruiz CA, Andreas S, Lewis KE, Tonnesen P, van Schayck CP, Hajek P, et al. Statement on smoking cessation in COPD and other pulmonary diseases and in smokers with comorbidities who find it difficult to quit. European Respiratory Journal. 2015;46(1):61-79.
89. van Eerd EA, van der Meer RM, van Schayck OC, Kotz D. Smoking cessation for people with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2016(8):CD010744.
90. Executive HaS. Health monitoring for chronic obstructive pulmonary disease 2006 [Available from: https://www.hse.gov.uk/pubns/guidance/g401.pdf.
91. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet. 2000;355(9201):362-8.
92. Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. Thorax. 2001;56(10):779-84.
93. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2015(2).
94. Puhan MA, Gimeno-Santos E, Cates CJ, Troosters T. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2016(12).
95. Bolton CE, Bevan-Smith EF, Blakey JD, Crowe P, Elkin SL, Garrod R, et al. British Thoracic Society guideline on pulmonary rehabilitation in adults. Thorax. 2013;68 Suppl 2:ii1-30.
96. Lahham A, Holland AE. The Need for Expanding Pulmonary Rehabilitation Services. Life. 2021;11(11):1236.

97. Stone PW, Hickman K, Steiner MC, Roberts CM, Quint JK, Singh SJ. Predictors of referral to pulmonary rehabilitation from UK primary care. International Journal of Chronic Obstructive Pulmonary Disease. 2020:2941-52.
98. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2017(7).
99. Davidson AC, Banham S, Elliott M, Kennedy D, Gelder C, Glossop A, et al. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016;71(Suppl 2):ii1-ii35.
100. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. European Respiratory Journal. 2017;50(2):1602426.
101. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, et al. Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial. JAMA. 2017;317(21):2177-86.
102. Cooper JD. The history of surgical procedures for emphysema. Ann Thorac Surg. 1997;63(2):312-9.
103. Meyers B, Patterson GA. Chronic obstructive pulmonary disease• 10: Bullectomy, lung volume reduction surgery, and transplantation for patients with chronic obstructive pulmonary disease. Thorax. 2003;58(7):634-8.
104. 201, Criner GJ. Surgical Approaches to Treating Emphysema: Lung Volume Reduction Surgery, Bullectomy, and Lung Transplantation. Semin Respir Crit Care Med. 2015;36(4):592-608.
105. Krishnamohan P, Shen KR, Wigle DA, Allen MS, Nichols FC, Cassivi SD, et al. Bullectomy for Symptomatic or Complicated Giant Lung Bullae. The Annals of Thoracic Surgery. 2014;97(2):425-31.
106. National Institute for Health and Care Excellence. Lung volume reduction surgery for advanced emphysema 2005 [Available from: https://www.nice.org.uk/guidance/ipg114/chapter/1-Guidance.
107. Criner GJ, Cordova F, Sternberg AL, Martinez FJ. The National Emphysema Treatment Trial (NETT) Part II: Lessons learned about lung volume reduction surgery. Am J Respir Crit Care Med. 2011;184(8):881-93.
108. Criner GJ, Sue R, Wright S, Dransfield M, Rivas-Perez H, Wiese T, et al. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE). Am J Respir Crit Care Med. 2018;198(9):1151-64.
109. Excellence NIfHaC. Endobronchial valve insertion to reduce lung volume in emphysema 2017 [Available from: https://www.nice.org.uk/guidance/ipg600.
110. Hardy JD, Webb WR, Dalton ML, Jr., Walker GR, Jr. Lung Homotransplantation in Man. JAMA. 1963;186:1065-74.
111. Siddiqui FM, Diamond JM. Lung transplantation for chronic obstructive pulmonary disease: past, present, and future directions. Curr Opin Pulm Med. 2018;24(2):199-204.
112. Stavem K, Bjortuft O, Borgan O, Geiran O, Boe J. Lung transplantation in patients with chronic obstructive pulmonary disease in a national cohort is without obvious survival benefit. J Heart Lung Transplant. 2006;25(1):75-84.
113. The International Society for Heart and Lung Transplantation. Post transplant survival and rejection 2019 [Available from: https://ishltregistries.org/registries/slides.asp.
114. Leard LE, Holm AM, Valapour M, Glanville AR, Attawar S, Aversa M, et al. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. The Journal of Heart and Lung Transplantation. 2021;40(11):1349-79.
115. Transplant NBa. Organ donation and transplantation activity report 2018/19. 2019.

116. Hardman G, Sutcliffe R, Hogg R, Mumford L, Grocott L, Mead-Regan SJ, et al. The impact of the SARS-CoV-2 pandemic and COVID-19 on lung transplantation in the UK: Lessons learned from the first wave. Clinical transplantation. 2021;35(3):e14210.
117. Cazzola M, Santangelo G, Piccolo A, Salzillo A, Matera MG, D'Amato G, et al. Effect of salmeterol and formoterol in patients with chronic obstructive pulmonary disease. Pulm Pharmacol. 1994;7(2):103-7.
118. Vincken W, van Noord JA, Greefhorst AP, Bantje TA, Kesten S, Korducki L, et al. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. Eur Respir J. 2002;19(2):209-16.
119. Tattersfield AE. Current issues with beta2-adrenoceptor agonists: historical background. Clin Rev Allergy Immunol. 2006;31(2-3):107-18.
120. i.pinimg.com. The distribution of beta receptors in the body 2023 [Available from: https://i.pinimg.com/originals/a6/e2/e4/a6e2e403fd20cec1f4aaaa23a2508c08.png.
121. Care AAoR. Respiratory care: A journey through time. 2020.
122. freeart.com. Thebeta-2-adrenergic receptor a cell membrane 2023 [Available from: https://images.freeart.com/comp/art-print/fa44046867/the-beta-2-adrenergic-receptor-a-cell-membrane-spanning-beta-adrenergic-receptor-which-mediates-physiologic-responses-such-as-smooth-muscle-relaxation-and-bronchodilation-3d-rendering.jpg?pw=10.0&ph=8.0&fit=True&print_finish=matte&size=mobile390.
123. Tattersfield AE, McNicol MW. Salbutamol and isoproterenol. A double-blind trial to compare bronchodilator and cardiovascular activity. N Engl J Med. 1969;281(24):1323-6.
124. Larsson S, Svedmyr N. Bronchodilating Effect and Side Effects of Beta2-Adrenoceptor Stimulants by Different Modes of Administration (Tablets, Metered Aerosol, and Combinations Thereof). American Review of Respiratory Disease. 1977;116(5):861-9.
125. Barnes P. Therapeutics in respiratory disease / Peter J. Barnes ... [et al.], with contribution by Robert F. Miller. Edinburgh

New York: Edinburgh

New York : Churchill Livingstone; 1994.
126. Cazzola M, Molimard M. The scientific rationale for combining long-acting beta2-agonists and muscarinic antagonists in COPD. Pulm Pharmacol Ther. 2010;23(4):257-67.
127. Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. Am J Respir Crit Care Med. 1997;155(4):1283-9.
128. Boyd G, Morice A, Pounsford J, Siebert M, Peslis N, Crawford C. An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). European Respiratory Journal. 1997;10(4):815-21.
129. Dahl R, Chung KF, Buhl R, Magnussen H, Nonikov V, Jack D, et al. Efficacy of a new once-daily long-acting inhaled β₂-agonist indacaterol versus twice-daily formoterol in COPD. Thorax. 2010;65(6):473-9.
130. SIGN158:British guideline on the management of asthma: Scottish Intercollegiate Guidelines Network; 2019.
131. Scullion JE. The development of anticholinergics in the management of COPD. Int J Chron Obstruct Pulmon Dis. 2007;2(1):33-40.
132. Poppius H, Salorinne Y. Comparative Trial of a New Anticholinergic Bronchodilator, Sch 1000, and Salbutamol in Chronic Bronchitis. British Medical Journal. 1973;4(5885):134-6.
133. studyingmed.com. Respiratory pharmacology: chronic airway limitation,. 2020.
134. Matera MG, Page CP, Calzetta L, Rogliani P, Cazzola M. Pharmacology and Therapeutics of Bronchodilators Revisited. Pharmacological Reviews. 2020;72(1):218-52.
135. Cheyne L, Irvin-Sellers MJ, White J. Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2015(9).

136. Poppius H, Salorinne Y. Comparative Trial of a New Anticholinergic Bronchodilator, Sch 1000, and Salbutamol in Chronic Bronchitis. BMJ. 1973;4(5885):134-6.
137. Fischer Jn, Ganellin CR, Rotella DP. Analogue-based drug discovery III edited by János Fischer, C. Robin Ganellin and David P. Rotella. Weinheim, Germany: Weinheim, Germany : Wiley-VCH; 2013.
138. Beier J, Kirsten A-M, Mróz R, Segarra R, Chuecos F, Caracta C, et al. Efficacy and Safety of Aclidinium Bromide Compared with Placebo and Tiotropium in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease: Results from a 6-week, Randomized, Controlled Phase Iiib Study. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2013;10(4):511-22.
139. Karabis A, Lindner L, Mocarski M, Huisman E, Greening A. Comparative efficacy of aclidinium versus glycopyrronium and tiotropium, as maintenance treatment of moderate to severe COPD patients: a systematic review and network meta-analysis. International journal of chronic obstructive pulmonary disease. 2013;8:405-23.
140. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease. New England Journal of Medicine. 2008;359(15):1543-54.
141. Easton PA, Jadue C, Dhingra S, Anthonisen NR. A comparison of the bronchodilating effects of a beta-2 adrenergic agent (albuterol) and an anticholinergic agent (ipratropium bromide), given by aerosol alone or in sequence. N Engl J Med. 1986;315(12):735-9.
142. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. COMBIVENT Inhalation Aerosol Study Group. Chest. 1994;105(5):1411-9.
143. Konno S, Makita H, Hasegawa M, Nasuhara Y, Nagai K, Betsuyaku T, et al. Beta2-adrenergic receptor polymorphisms as a determinant of preferential bronchodilator responses to beta2-agonist and anticholinergic agents in Japanese patients with chronic obstructive pulmonary disease. Pharmacogenet Genomics. 2011;21(11):687-93.
144. Barnes PJ. Corticosteroid resistance in airway disease. Proc Am Thorac Soc. 2004;1(3):264-8.
145. Nardini S, Camiciottoli G, Locicero S, Maselli R, Pasqua F, Passalacqua G, et al. COPD: maximization of bronchodilation. Multidiscip Respir Med. 2014;9(1):50.
146. Gardenhire DS. Rau's Respiratory Care Pharmacology-E-Book: Elsevier Health Sciences; 2015.
147. Pelaia G, Maselli R, Gallelli L. Pharmacologic rationale, efficacy and safety of the fixed-dose co-formulation of indacaterol and glycopyrronium. Multidiscip Respir Med. 2014;9(1):64.
148. Oba Y, Keeney E, Ghatehorde N, Dias S. Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD) : A systematic review and network meta-analysis. 2018.
149. Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005(4):CD001744.
150. Hardinge M, Annandale J, Bourne S, Cooper B, Evans A, Freeman D, et al. British Thoracic Society guidelines for home oxygen use in adults. Thorax. 2015;70 Suppl 1:i1-43.
151. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med. 1980;93(3):391-8.
152. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet. 1981;1(8222):681-6.
153. Long-Term Oxygen Treatment Trial Research G, Albert RK, Au DH, Blackford AL, Casaburi R, Cooper JA, Jr., et al. A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation. N Engl J Med. 2016;375(17):1617-27.
154. Rabe KF. Update on roflumilast, a phosphodiesterase 4 inhibitor for the treatment of chronic obstructive pulmonary disease. British journal of pharmacology. 2011;163(1):53-67.
155. Martinez FJ, Calverley PM, Goehring U-M, Brose M, Fabbri LM, Rabe KF. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by

combination therapy (REACT): a multicentre randomised controlled trial. The Lancet. 2015;385(9971):857-66.
156. Janjua S, Fortescue R, Poole P. Phosphodiesterase-4 inhibitors for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2020(5).
157. Jaffé A, Bush A. Anti-inflammatory effects of macrolides in lung disease. Pediatric pulmonology. 2001;31(6):464-73.
158. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA, Jr., Criner GJ, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med. 2011;365(8):689-98.
159. Seemungal TA, Wilkinson TM, Hurst JR, Perera WR, Sapsford RJ, Wedzicha JA. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. Am J Respir Crit Care Med. 2008;178(11):1139-47.
160. Uzun S, Djamin RS, Kluytmans JA, Mulder PG, van't Veer NE, Ermens AA, et al. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. The Lancet Respiratory Medicine. 2014;2(5):361-8.
161. Han MK, Tayob N, Murray S, Dransfield MT, Washko G, Scanlon PD, et al. Predictors of chronic obstructive pulmonary disease exacerbation reduction in response to daily azithromycin therapy. Am J Respir Crit Care Med. 2014;189(12):1503-8.
162. Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The Efficacy and Cost Effectiveness of Vaccination against Influenza among Elderly Persons Living in the Community. New England Journal of Medicine. 1994;331(12):778-84.
163. Kopsaftis Z, Wood-Baker R, Poole P. Influenza vaccine for chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2018;6(6):Cd002733.
164. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012;67(1):71-9.
165. Bonten Marc JM, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults. The New England Journal of Medicine. 2015;372(12):1114-25.
166. Alfageme I, Vazquez R, Reyes N, Muñoz J, Fernández A, Hernandez M, et al. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. Thorax. 2006;61(3):189-95.
167. Walters JA, Tang JN, Poole P, Wood-Baker R. Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017;1(1):Cd001390.
168. Excellence NIfHaC. Chronic obstructive pulmonary disease in over 16s: diagnosis and management 2019 [Available from: https://www.nice.org.uk/guidance/ng115/resources/chronic-obstructive-pulmonary-disease-in-over-16s-diagnosis-and-management-pdf-66141600098245.
169. Stone S, Malanga GA, Capella T. Corticosteroids: Review of the history, the effectiveness, and adverse effects in the treatment of joint pain. Pain Physician. 2021;24(S1):S233.
170. Crompton G. A brief history of inhaled asthma therapy over the last fifty years. Prim Care Respir J. 2006;15(6):326-31.
171. Tashkin DP, Strange C. Inhaled corticosteroids for chronic obstructive pulmonary disease: what is their role in therapy? Int J Chron Obstruct Pulmon Dis. 2018;13:2587-601.
172. Finkelstein R, Fraser RS, Ghezzo H, Cosio MG. Alveolar inflammation and its relation to emphysema in smokers. Am J Respir Crit Care Med. 1995;152(5 Pt 1):1666-72.
173. Mendella L, Manfreda J, Warren C, Anthonisen N. Steroid response in stable chronic obstructive pulmonary disease. Annals of internal medicine. 1982;96(1):17-21.
174. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, et al. Treatable traits: toward precision medicine of chronic airway diseases. European Respiratory Journal. 2016;47(2):410-9.
175. Diamant Z, Brusselle G, Russell RE. Toward effective prescription of inhaled corticosteroids in chronic airway disease. Int J Chron Obstruct Pulmon Dis. 2018;13:3419-24.

176. Boardman C, Chachi L, Gavrila A, Keenan CR, Perry MM, Xia YC, et al. Mechanisms of glucocorticoid action and insensitivity in airways disease. Pulm Pharmacol Ther. 2014;29(2):129-43.
177. Williams DM. Clinical Pharmacology of Corticosteroids. Respir Care. 2018;63(6):655-70.
178. http://img.medscapestatic.com/. Proposed synergy of LABA and inhaled CS 2023 [Available from: http://img.medscapestatic.com/fullsize/migrated/editorial/cmelive/2007/6294/images/slide20.gif.
179. Weir D, Gove R, Robertson A, Burge PS. Corticosteroid trials in non-asthmatic chronic airflow obstruction: a comparison of oral prednisolone and inhaled beclomethasone dipropionate. Thorax. 1990;45(2):112-7.
180. Thompson AB, Mueller MB, Heires AJ, Bohling TL, Daughton D, Yancey SW, et al. Aerosolized beclomethasone in chronic bronchitis. Improved pulmonary function and diminished airway inflammation. Am Rev Respir Dis. 1992;146(2):389-95.
181. Auffarth B, Postma D, De Monchy J, Van der Mark T, Boorsma M, Koeter G. Effects of inhaled budesonide on spirometric values, reversibility, airway responsiveness, and cough threshold in smokers with chronic obstructive lung disease. Thorax. 1991;46(5):372-7.
182. Burge PS. EUROSCOP, ISOLDE and the Copenhagen city lung study. Thorax. 1999;54(4):287-8.
183. Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, Efthimiou J, et al. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. The Lancet. 1998;351(9105):773-80.
184. Pauwels RA, Löfdahl C-G, Laitinen LA, Schouten JP, Postma DS, Pride NB, et al. Long-Term Treatment with Inhaled Budesonide in Persons with Mild Chronic Obstructive Pulmonary Disease Who Continue Smoking. New England Journal of Medicine. 1999;340(25):1948-53.
185. Burge PS, Calverley PMA, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ. 2000;320(7245):1297-303.
186. Group LHSR. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. New England Journal of Medicine. 2000;343(26):1902-9.
187. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease. New England Journal of Medicine. 2007;356(8):775-89.
188. Vestbo J, Anderson JA, Brook RD, Calverley PMA, Celli BR, Crim C, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. The Lancet. 2016;387(10030):1817-26.
189. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2012(7).
190. Suissa S. Inhaled corticosteroids preventing pneumonia mortality: paradox or selection bias? Eur Respir J. 2019;53(2).
191. Singh D, Papi A, Corradi M, Pavlišová I, Montagna I, Francisco C, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. Lancet. 2016;388(10048):963-73.
192. Bourbeau J, Bafadhel M, Barnes NC, Compton C, Di Boscio V, Lipson DA, et al. Benefit/Risk Profile of Single-Inhaler Triple Therapy in COPD. Int J Chron Obstruct Pulmon Dis. 2021;16:499-517.
193. Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. Lancet. 2018;391(10125):1076-84.
194. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. The New England Journal of Medicine. 2018;378(18):1671-80.

195. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, et al. Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. New England Journal of Medicine. 2020;383(1):35-48.
196. Buhl R, Criée CP, Kardos P, Vogelmeier CF, Kostikas K, Lossi NS, et al. Dual bronchodilation vs triple therapy in the "real-life" COPD DACCORD study. Int J Chron Obstruct Pulmon Dis. 2018;13:2557-68.
197. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, et al. Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. N Engl J Med. 2020;383(1):35-48.
198. Suissa S. Perplexing mortality data from triple therapy trials in COPD. Lancet Respir Med. 2021;9(7):684-5.
199. Suissa S, Dell'Aniello S, Ernst P. Triple inhaler versus dual bronchodilator therapy in COPD: real-world effectiveness on mortality. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2022;19(1):1-9.
200. Suissa S, Dell'Aniello S, Ernst P. Single-Inhaler Triple versus Dual Bronchodilator Therapy in COPD: Real-World Comparative Effectiveness and Safety. Int J Chron Obstruct Pulmon Dis. 2022;17:1975-86.
201. Yu AP, Guerin A, de Leon DP, Ramakrishnan K, Wu EQ, Mocarski M, et al. Clinical and economic outcomes of multiple versus single long-acting inhalers in COPD. Respiratory medicine. 2011;105(12):1861-71.
202. Halpin DMG, Worsley S, Ismaila AS, Beeh K-M, Midwinter D, Kocks JWH, et al. INTREPID: single- versus multiple-inhaler triple therapy for COPD in usual clinical practice. ERJ Open Research. 2021;7(2):00950-2020.
203. Bogart M, Wu B, Germain G, Laliberté F, MacKnight S, Jung Y, et al. Real-world adherence to single-inhaler vs multiple-inhaler triple therapy among patients with COPD in a commercially insured US population. Chest. 2020;158(4):A1773-A4.
204. Halpin DM, Rothnie KJ, Banks V, Czira A, Compton C, Wood R, et al. Comparative Adherence and Persistence of Single-and Multiple-Inhaler Triple Therapies Among Patients with Chronic Obstructive Pulmonary Disease in an English Real-World Primary Care Setting. International Journal of Chronic Obstructive Pulmonary Disease. 2022;17:2417-29.
205. Alcázar-Navarrete B, Jamart L, Sánchez-Covisa J, Juárez M, Graefenhain R, Sicras-Mainar A. Clinical Characteristics, Treatment Persistence, and Outcomes Among Patients With COPD Treated With Single- or Multiple-Inhaler Triple Therapy: A Retrospective Analysis in Spain. Chest. 2022.
206. Comittee JF. British National Formulary 72. London: Pharmaceutical Press; 2016.
207. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. The Cochrane database of systematic reviews. 2012;7:CD002991.
208. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008;177(1):19-26.
209. Price D, Yawn B, Brusselle G, Rossi A. Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD. Primary care respiratory journal : journal of the General Practice Airways Group. 2013;22(1):92-100.
210. Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. The Cochrane database of systematic reviews. 2012;9:CD006829.
211. Crim C, Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. Eur Respir J. 2009;34(3):641-7.
212. Suissa S. Author's response to letter on number needed to treat in COPD: exacerbations versus pneumonias. Thorax. 2013;68(9):882-3.

213. Kim JH, Park JS, Kim KH, Jeong HC, Kim EK, Lee JH. Inhaled corticosteroid is associated with an increased risk of TB in patients with COPD. Chest. 2013;143(4):1018-24.
214. Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. The New England journal of medicine. 2010;363(12):1128-38.
215. Agusti A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PloS one. 2012;7(5):e37483.
216. Vanfleteren LE, Spruit MA, Groenen M, Gaffron S, van Empel VP, Bruijnzeel PL, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;187(7):728-35.
217. Barnes PJ. Inhaled corticosteroids in COPD: a controversy. Respiration; international review of thoracic diseases. 2010;80(2):89-95.
218. White P, Thornton H, Pinnock H, Georgopoulou S, Booth HP. Overtreatment of COPD with inhaled corticosteroids--implications for safety and costs: cross-sectional observational study. PloS one. 2013;8(10):e75221.
219. Price D, West D, Brusselle G, Gruffydd-Jones K, Jones R, Miravitlles M, et al. Management of COPD in the UK primary-care setting: an analysis of real-life prescribing patterns. International journal of chronic obstructive pulmonary disease. 2014;9:889-904.
220. Wedzicha JA, Decramer M, Seemungal TA. The role of bronchodilator treatment in the prevention of exacerbations of COPD. Eur Respir J. 2012;40(6):1545-54.
221. Wedzicha JA, Decramer M, Ficker JH, Niewoehner DE, Sandstrom T, Taylor AF, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. The Lancet Respiratory medicine. 2013;1(3):199-209.
222. Singh D, Jones PW, Bateman ED, Korn S, Serra C, Molins E, et al. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. BMC pulmonary medicine. 2014;14:178.
223. D'Urzo AD, Rennard SI, Kerwin EM, Mergel V, Leselbaum AR, Caracta CF, et al. Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study. Respiratory research. 2014;15:123.
224. Magnussen H, Disse B, Rodriguez-Roisin R, Kirsten A, Watz H, Tetzlaff K, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. N Engl J Med. 2014;371(14):1285-94.
225. Jarad NA, Wedzicha JA, Burge PS, Calverley PM. An observational study of inhaled corticosteroid withdrawal in stable chronic obstructive pulmonary disease. ISOLDE Study Group. Respir Med. 1999;93(3):161-6.
226. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. N Engl J Med. 2016;374(23):2222-34.
227. Charlesworth G, Burnell K, Hoe J, Orrell M, Russell I. Acceptance checklist for clinical effectiveness pilot trials: a systematic approach. BMC medical research methodology. 2013;13:78.
228. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648-54.
229. Simon Pickard A, Wilke C, Jung E, Patel S, Stavem K, Lee TA. Use of a preference-based measure of health (EQ-5D) in COPD and asthma. Respiratory Medicine. 2008;102(4):519-36.
230. 2014/15 General Medical Services (GMS) Contract Quality and Outcomes Framework (QOF). London: British Medical Association; 2014.
231. Sylvester KP, Clayton N, Cliff I, Hepple M, Kendrick A, Kirkby J, et al. ARTP statement on pulmonary function testing 2020. BMJ Open Respiratory Research. 2020;7(1):e000575.
232. Breathe R. Find an inhaler UK2023 [Available from: https://www.rightbreathe.com/medicines.

233. Hosmer Jr DW, Lemeshow S, Sturdivant RX. Applied logistic regression: John Wiley & Sons; 2013.
234. Brusselle G, Price D, Gruffydd-Jones K, Miravitlles M, Keininger DL, Stewart R, et al. The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK. Int J Chron Obstruct Pulmon Dis. 2015;10:2207-17.
235. Singh D, Agusti A, Martinez FJ, Papi A, Pavord ID, Wedzicha JA, et al. Blood Eosinophils and Chronic Obstructive Pulmonary Disease: A Global Initiative for Chronic Obstructive Lung Disease Science Committee 2022 Review. American Journal of Respiratory and Critical Care Medicine. 2022;206(1):17-24.
236. Chalmers JD, Laska IF, Franssen FME, Janssens W, Pavord I, Rigau D, et al. Withdrawal of inhaled corticosteroids in COPD: a European Respiratory Society guideline. European Respiratory Journal. 2020;55(6):2000351.