TITLE: sTep dOWn inhalers in the reAl woRID (TOWARD)

VERSION 5: 14TH FEBRUARY 2017

AUTHORS: Joe Annandale (2), Amit Benjamin (3), Teresa Ching (4), Kevin Gruffydd-Jones (5), Paul Neil (3), Patrick Flood-Page (6), James Calvert (7), Hayley Hutchings (1), Keir E Lewis (1,2).

AFFILIATIONS:

1. Swansea University Medical School, Swansea University , Swansea, Wales, SA2 8PP.
2. Respiratory Unit, Prince Philip Hospital, Hywel Dda University Health Board, Wales, SA14 8QF.
3. Respiratory Unit, Royal Glamorgan Hospital, Cwm Taf University Health Board, Wales, CF72 8XR.
4. Respiratory Unit, Glan Clwyd Hospital, Betsi Cadwallader University Health Board, Wales, LL18 5UJ.
5. Box Surgery, Wiltshire, England, SN13 8NA.
6. Respiratory Unit, Royal Gwent Hospital, Aneurin Bevan University Health Board, Wales.
7. Department of Respiratory Medicine, Southmead Hospital, North Bristol NHS Trust, England, BS10 5NB.

ABSTRACT:

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

Recent randomised controlled studies suggest that reducing then withdrawing ICS is not associated with increased exacerbations and LABA+LAMAs alone may even show superior efficacy to ICS/LABA combinations. Future guidelines will be informed by these studies but the feasibility and effects of stopping ICS in a real-life setting have not been tested.

We plan to undertake a feasibility study to determine whether a full study examining the direct switch from triple (ICS+ LABA+LAMA) regimes to dual (LABA+LAMA) regimes in the real world is possible. Initially we will approach 80 people with stable COPD, in an

interventional, open-label study. We will 1) Evaluate the infrastructure necessary to perform a future definitive study, including a Study Management Group /Data Management Committee 2) Test the feasibility of the proposed study design 3) Assess the processes of patient recruitment, consent and reasons for non-participation4) Assess the quantity and potential patterns of missing data 5) Estimate potential cost savings and costs of reviews 6) Monitor any early safety data (exacerbation rates).
We will then be better informed to decide whether a multi-centre step-down intervention is possible by formal assessment of feasibility study findings against pre-set progression criteria. If the full definitive study is deemed feasible then potential research sites across UK will be contacted for participation and a full study protocol and funding applications will be completed

INTRODUCTION:

Chronic obstructive pulmonary disease (COPD) is an umbrella term for a group of lung conditions characterized by airways inflammation, small airway obstruction and progressive deterioration in lung function. (1) Symptoms include breathlessness, cough, sputum production, fatigue and chest pain but COPD is increasingly recognised as a multi-system disease with direct and indirect effects on the musculoskeletal and cardiovascular systems as well as low mood and psychological problems. The diagnosis is confirmed clinically and then by using physiological measures of airway obstruction (spirometry), with severity based on a combination of the reduction in the forced expiratory volume in 1 second (FEV_1), breathlessness symptoms and future risk (exacerbations). (1)

The most recent prevalence studies estimate that 11.8% of men, and 8.5% of women worldwide are affected by COPD. (2) 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. (3, 4) This is a likely underestimate 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 (5), exposure to biomass fuels (6), early pre and post-natal lung development (7) and genetic susceptibility (8, 9) all contributing.

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 (1, 10, 11) and is predicted to become the third highest cause of mortality by 2020. (2) There are no curative treatments and the contributory roles of co-morbidities and poor social circumstances are also increasingly recognized. (12, 13)

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. Moderate exacerbations are those requiring parental steroids or antibiotics and severe exacerbations are those requiring admission to hospital for at least 24 hours (1) 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. (14) US data showed that in 1 year, COPD caused 1.5 million emergency department attendances, 726, 000 hospital admissions and 119, 000 deaths. (15) Exacerbations are associated with higher mortality rates in COPD (16-18), more rapid decline in lung function (19) and worsening health status. (20, 21)

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. (1) 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 ICs to short acting bronchodilators (22) but although longer term clinical studies such as TORCH showed a reduction in exacerbations (23) 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 (24), a Cochrane review (25) and literature reviews (26) - 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, (27) oral candidiasis, (27, 28) increased risk of pneumonia, (27-30) osteoporosis, early onset diabetes, cataracts, (27) and tuberculosis. (31) The TORCH study itself demonstrated more side effects than placebo and LABA alone-particularly increased pneumonia risk that was statistically significant and clinically important. (29)

It is important to note that sub-group analysis of TORCH and other studies suggest that ICS may benefit some groups of patients. (28) Certain COPD phenotypes e.g. characterized by repeated exacerbations (32), inflammatory patterns (33) and co-morbidities (34) 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. (35) 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. (36) 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. (37)

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 (38). 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 (38-41) 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 (FEV1<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 FEV1 of around 60 ml. (42) 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) (43). However, most recently, a 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 of ICS/LABA. 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. (44)

Respiratory medicines (inhalers) are the largest proportion of the Primary Care prescribing budget in the UK. The tables below illustrate the costs of the most commonly prescribed inhalers for COPD in Wales (ps://www.medicinescomplete.com/mc/bnf/current/):

	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 that organisation would potentially save £36,400- £72,600. Many people will be prescribed these inhalers for the rest of their lives averaging 10-20 years.

In summary, the small possible benefit, proven side effects, high financial cost and now better bronchodilator alternatives mean the risk: benefit profile of ICS needs to be carefully examined in a real world setting where

1. uptake of an inhaler-step-down by staff and patients (not in highly selected populations supported by pharma funding).

2. All 4 currently licensed LABA+LAMA combinations would help inform prescribers that we are seeing a class effect (rather than single drugs).

AIMS:

To establish the feasibility of stopping inhaled steroids and switching or maintaining dual bronchodilation in one visit - in the real world, for people with COPD.

METHODS:

Type: Feasibility study.

The feasibility study will be registered on clinicalstudys.gov.

1. **Participants:**

80 patients with stable COPD prescribed a combination of ICS+LABA+LAMA.
The sample size for this feasibility study (n=80) is the minimum number of participants considered necessary to test the processes of data collection, and based on the recommendations of Lancaster with respect to the number of patients required to yield meaningful estimates of parameters of interest.(45)

Inclusion Criteria: GP diagnosis of COPD (quality and outcomes framework (QoF) diagnostic code) (46); current or ex-smokers with at least a 10-pack year smoking history; age over 40 years old, post bronchodilator FEV_1 <80% predicted and FEV/FVC ratio<70%; prescribed any triple combination of LABA+ LAMA+ICS; any co-morbidity.

Exclusion criteria: unwilling or unable to sign informed consent; GP or hospital diagnosis of asthma; features to suggest asthma on screening questionnaire (large variability in symptoms, atopy, nasal polyps, <10 pack year smoking and peripheral blood eosinophil count >600 mm^3); recent severe exacerbation of COPD (needing admission to hospital for > 24 hours) within the last 6 weeks; inability to use inhalers (e.g. neuromuscular disability); life expectancy less than 1 year.

2. Procedure:

Switch protocol:

Eligible subjects will be identified through screening of primary care records by prescribing pharmacists and practice nurses (own clinical teams). Those prescribed triple therapy and with no GP diagnosis of asthma, will be posted an Invitation letter. This will be followed-up with a reminder letter and they will be invited for review by a GP practice nurse, respiratory specialist nurse or community-based pharmacist.

VISIT 1 (0 weeks): Consent and Screening history, demographics, spirometry (FEV) and result of any previous full blood count (eosinophil count) are recorded (Appendix 1). They will complete the COPD assessment Test (CAT) and Quality of life Questionnaire, EQ-5D (Appendix 2).

Participants are shown the four currently available LABA/LAMA combination inhalers and instructed on their use. The clinical specialist will use standard prompts in an effort to demonstrate the inhalers in an unbiased way (see Appendix 3). The participants will choose:

-Ultibro® (Breezehaler) or Duaklir® (Genuair device) or Anorro® (Ellipta device) or Spioloto® (Respimat) and they will be prescribed that inhaler

VISIT 2 (4 weeks): Check exacerbation history (need for oral steroids, healthcare contacts), inhaler type (whether still dual or revert back to triple), usage (counter) and demonstration of technique (critical error count), FEV1, CAT, EQ5D.

VISIT 3 (12 weeks): Check exacerbation history (need for oral steroids, healthcare contacts), inhaler type (whether still dual or revert back to triple), usage (counter) and demonstration of technique (critical error count), FEV1, CAT, EQ5D.

VISIT 4 (26 weeks): Check exacerbation history (need for oral steroids, healthcare contacts), inhaler type (whether still dual or revert back to triple), usage (counter) and demonstration of technique (critical error count), FEV1, CAT, EQ5D.

VISIT 5 (52 weeks): Check exacerbation history (need for oral steroids, healthcare contacts), inhaler type (whether still dual or revert back to triple), usage (counter) and demonstration of technique (critical error count), FEV1, CAT, EQ5D.

Review protocol:

To assess the feasibility to support continuation to the full definitive study, the following criteria will be assessed by the Data Monitoring Committee, using the ACCEPT model (Charlesworth et al, 2013)(47)

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 inhaler switch during intervention period

3) Outcomes:

• Overall mean number of exacerbations is not 20% more than those receiving standard care

• > 60% return rate of QoL questionnaires at 6 months

• 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

For the purposes of this feasibility study we will explore descriptively the key parameters of interest. These include:

- The proportion of patients who agree to switch inhalers.
- The proportion of patients undergoing switch who experience exacerbations / toxicities.
- The proportion of patients for whom we can collect outcomes for at 1, 4 and 12 weeks post-inhaler switch (i.e. follow up rates):
    - The response rates to the questionnaires.
    - Adherence / compliance rates.
- The standard deviation of the QoL measures that are proposed for the definitive study.
- The effect sizes for exacerbation rates and QoL scores

Although there is no control group, this size would inform a sample size calculation to ensure adequate power to detect a significant difference in exacerbations, QoL and inhaler costs compared to the year prior. This reduces the chance of a type 2 error for increased safety for exacerbations / mortality (i.e. failing to detect an effect that is present i.e. false negative).

If these feasibility criteria are met with these 80 patients over 6 months, we plan to continue recruitment of up to 1500 patients using GP databases, hospital databases and pharmacy prescribers in a phased scaled-up study from up to 4 Welsh Health Boards and an English NHS Trust (North Bristol) and follow them for a longer period of 1 year

Together these organisations cover a population over 1.5 million people.

In this larger study, a safety and data monitoring committee will also meet based on criteria derived from the feasibility study. The study will be reviewed / halted if we see an exacerbation rate more than 20% above the previous year or any systematic suspected adverse events (clinician's discretion).

3. **Statistics:**

Analysis will be performed using SPSS version 22.2 (Chicago, Illinois).

PRIMARY OBJECTIVE

To establish whether a future, definitive intervention study of removing ICS from a triple combination inhaled regimen is feasible in the real world.

The analysis for this feasibility study will not examine differences in outcomes but may present some descriptive information that could be used to inform extent of participation, missing data, sample size for safety signals etc

Secondary Objectives:

- To set up and test the infrastructure necessary to perform a definitive study
- To test willingness of eligible participants to switch inhalers
- To quantify the number of participants required for a definitive study

- To test the ability to recruit, consent and retain participant to inhaler switch
- To qualitatively explore reasons for non-recruitment
- To test appropriateness and feasibility of collecting the proposed outcomes measures for a full study.

All secondary outcomes will be rehearsed during the feasibility study with a view to refining a) the process and b) inform the choice of outcomes for the main study. The ability to collect the following clinical, pathological, QoL and health economics data will be tested.

a) EQ-5D and CAT quality of life tools
b) Moderate-severe exacerbation rates (need for 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.

The definitive study will be designed to test:

Primary Outcome:

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.

SECONDARY OBJECTIVES

Secondary outcomes:

Effectiveness /safety:

1. Comparison of the number of moderate and severe exacerbations in those on LABA+LAMA over 52 weeks compared with their previous 52 weeks
2. Comparison of the number of moderate and severe exacerbations in those on LABA+LAMA over 52 weeks compared with those continuing triple therapy

3. Comparison of time to first exacerbation in those on LABA+LAMA over 52 weeks compared with those continuing triple therapy
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.
6. Proportions of patients choosing each LABA+LAMA device and some reasons why (See Appendix 3)
7. Comparison of total inhaler prescription costs 1 year prior and 1 year after switch
8. Estimate of cost-effectiveness of intervention based on changes in prescribing costs, other resource utilisation, together with changes in EQ-5D utilities and QALYs gained.

DISCUSSION

This is the first intervention that is generic to the classes of inhaled medications and driven by inhaler choice and not limited to any particular brand or device and hopefully inform real-world prudent prescribing and clinical guidelines.

This is both primary care and secondary care-based and is initially a feasibility study. For pragmatic studys, where generalisability or external validity is key, greater flexibility is written into study protocols to allow for 'real life' variation in procedures. (47)

TIMELINES: 33 months
3 months to appoint study coordinator and obtain ethics and R&D permissions.

12 months recruitment

12 months follow-up

6 months write-up and analysis

COSTS

Clinician time, chief investigator time in study design seeking ethics advice and overall clinical review is provided; community pharmacy time will be provided in each site.

Publication and printing costs (£2000) to be paid by Prof K Lewis' charitable account or further grant applications.For the definitive study we will seek funding for:

-A full-time clinical study coordinator 37.5 hours per week at Band 5 point 18 = £23,132 per year within Hywel Dda Health Board and Cwm Taf; for 2.5 years (1 year recruitment, 1 year follow-up, 6 months write-up and dissemination) **= 2x £57,830**

Travel Costs = £2000

-TOTAL circa £117, 660

REFERENCES

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. Molfino NA. Genetics of COPD. Chest. 2004;125(5):1929-40.
9. Wood AM, Stockley RA. Unifying the genetics, co-morbidities and management of COPD. Ther Adv Respir Dis. 2008;2(3):113-7.
10. 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.
11. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet. 1997;349(9061):1269-76.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.

19. 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.
20. 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.
21. Cote CG, Dordelly LJ, Celli BR. Impact of COPD exacerbations on patient-centered outcomes. Chest. 2007;131(3):696-704.
22. Burge PS, Calverley PM, 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 study. Bmj. 2000;320(7245):1297-303.
23. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. The New England journal of medicine. 2007;356(8):775-89.
24. Jen R, Rennard SI, Sin DD. Effects of inhaled corticosteroids on airway inflammation in chronic obstructive pulmonary disease: a systematic review and meta-analysis. International journal of chronic obstructive pulmonary disease. 2012;7:587-95.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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.
30. Suissa S. Author's response to letter on number needed to treat in COPD: exacerbations versus pneumonias. Thorax. 2013;68(9):882-3.
31. 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.
32. 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.
33. 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.
34. 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.
35. Barnes PJ. Inhaled corticosteroids in COPD: a controversy. Respiration; international review of thoracic diseases. 2010;80(2):89-95.
36. 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.

37. 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.
38. 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.
39. 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.
40. 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.
41. 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.
42. Magnussen H, Disse B, Rodriguez-Roisin R, Kirsten A, Watz H, Tetzlaff K, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. The New England journal of medicine. 2014;371(14):1285-94.
43. 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.
44. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. The New England journal of medicine. 2016;374(23):2222-34.
45. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. Journal of evaluation in clinical practice. 2004;10(2):307-12. Epub 2004/06/11.
46. 2014/15 General Medical Services (GMS) Contract Quality and Outcomes Framework (QOF). London: British Medical Association; 2014.
47. Charlesworth G, Burnell K, Hoe J, Orrell M, Russell I. Acceptance checklist for clinical effectiveness pilot studys: a systematic approach. BMC medical research methodology. 2013;13:78. Epub 2013/06/14.