Study protocol

Effectiveness of prescribing similar vs. dissimilar devices for COPD management

A historical cohort, UK database study comparing disease outcomes and adherence in patients with COPD prescribed similar inhaler devices (in terms of inhalation technique) vs those prescribed dissmilar devices

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TITLE	Effectiveness of prescribing similar vs. dissimilar devices for COPD management
Subtitle	A historical cohort, UK database study comparing disease outcomes and adherence in patients with COPD prescribed similar inhaler devices (in terms of inhalation technique) vs those prescribed dissimilar devices
Protocol version number	3
Study aims and objectives	Patients with COPD are often prescribed more than one inhaler device. This study aims to investigate whether the use of dissimilar inhaler devices (in terms of inhalation technique) for the delivery of therapies has negative impact on disease outcome and therapy adherence in patients with COPD.
Country of study	United Kingdom
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Contents

1.0 Background

A variety of inhaler devices are available for delivering treatments to patients with chronic obstructive pulmonary disease (COPD), and the methods of preparation and use vary between them [1]. The technique required to use the different devices correctly may be markedly different in terms of handling and inhalation technique (e.g. pressurised metered-dose inhalers [pMDI] versus dry powder inhalers [DPI]) [2].The differences in instructions for use can easily confuse patients and health providers alike, resulting in incorrect use of many inhalers. Correct inhaler use is fundamental for effective disease management [3].

Patients with COPD are often prescribed more than one inhaler device (e.g. for "relief" bronchodilator and maintenance therapy), which may lead to patient confusion in terms of correct inhalation technique for each device. If technique is poor, worse disease outcomes are expected due to reduced lung deposition of prescribed therapies [4, 5].

Recent studies have highlighted these potential problems of prescribing mixed inhaler devices, but studies have been restricted to asthma patients and either did not assess the impact of the devices on disease outcomes [4] or focused on a limited number of devices [4,5].

Given the growing number of inhaler devices available [6] and that patients with COPD often require multiple therapies for disease management [7], this study aims to:

- categorise inhaler devices commonly prescribed for COPD management, based on similarities in the inhalation technique required for their correct use

- review prescription patterns of inhaler devices for COPD management, focusing on co-prescriptions for different devices

- assess the impacts on disease outcomes and therapy adherence of prescribing dissimilar inhaler devices, in terms of inhalation technique, versus similar devices

2.0 Study aims and objectives

2.1 Study aims

Given that patients with COPD are often prescribed more than one inhaler device, this study aims to investigate whether the use of dissimilar inhaler devices (in terms of inhalation technique) for the delivery of therapies have negative impacts on disease outcome and therapy adherence in patients with COPD. This study will have two phases.

2.2 Study objectives

- **Phase 1:** Review of inhaler device prescription patterns and categorisation of devices (based on required inhalation technique) commonly prescribed for COPD management.
- **Phase 2:** Effectiveness of similar vs dissimilar devices
  - Compare the effectiveness (in terms of moderate and severe exacerbation prevention) of prescribing inhaler devices with similar inhalation techniques vs prescribing devices with dissimilar inhalation techniques in patients with COPD
  - Assess therapy adherence in patients with COPD prescribed inhaler devices with similar inhalation techniques* vs patients prescribed devices with dissimilar inhalation techniques

This protocol is for **Phase 2** of the study.

*As defined in phase 1 of the study and based on expert advice

3.0 Data source

3.1 Optimum Patient Care Research Database (OPCRD)

OPC extracts anonymous data from practices to perform reviews of their chronic respiratory services. Two types of anonymised patient data are typically collected:

(1) Routine clinical data

• OPC software interfaces with primary care practice management systems and extracts disease coding and prescribing information

(2) Questionnaires

• Patients identified as recipients of the respiratory service under review are invited to complete validated disease assessment questionnaires to better understand their current health status (and/or possible reasons for sub-optimal status)

• Anonymised questionnaires are assigned a unique code to aid matching routine data to questionnaire results

The OPC research database (OPCRD), which comprises the routine clinical and questionnaire data, has been approved by Trent Multi Centre Research Ethics Committee for clinical research use. The database includes data from over a million patients captured across more than 500 practices.

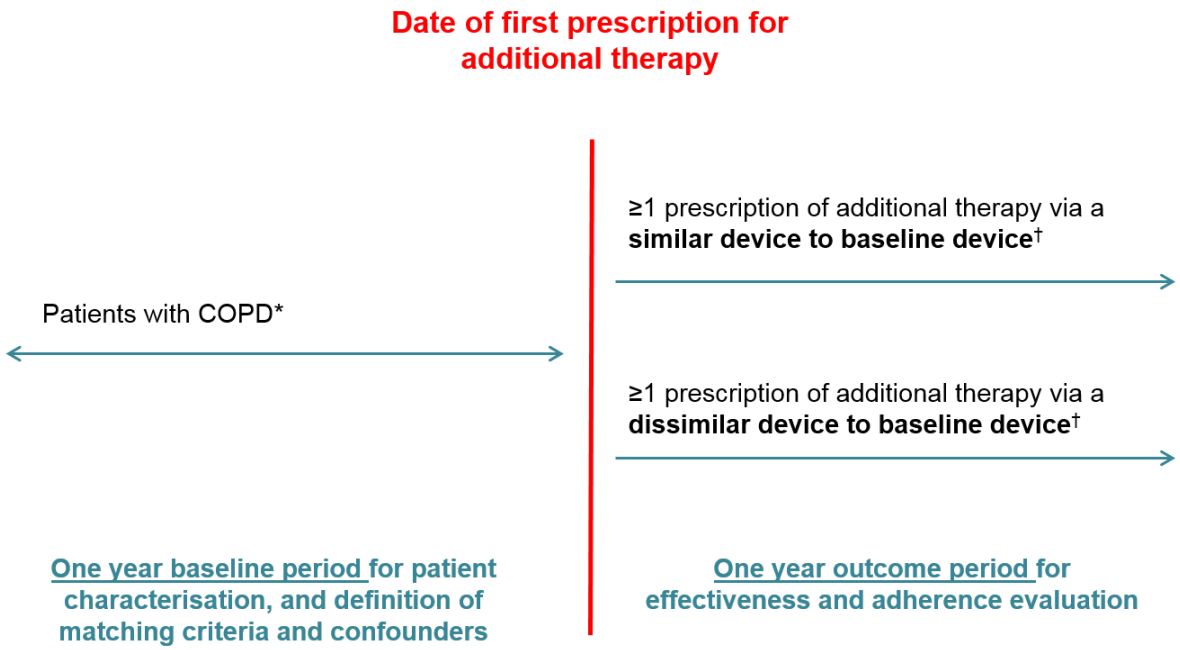
The anonymised, longitudinal patient data offers a high-quality data source for use in clinical, epidemiological and pharmaceutical research. It enables research to be carried out across a broad-range of respiratory areas and, in contrast to other medical research databases (e.g. the Clinical Practice Research Datalink [CPRD]), OPC data offers the additional dimension of patient reported outcomes.

4.0 Study design

This is a historical cohort, UK database study comparing disease outcomes and adherence in patients with COPD prescribed similar inhaler devices (in terms of inhalation technique) versus those prescribed dissimilar devices.

4.1 Study period

- **Phase 2** of the study will consist of a baseline and outcome period. The baseline period will be the period one year before the date of the patient's first prescription for additional therapy that may be for a similar or dissimilar device.



*Includes patients prescribed SABA (short-acting beta2-agonist), SAMA (short-acting muscarinic antagonist), LABA (long-acting beta2-agonist) or LAMA (long-acting muscarinic antagonist) as monotherapy or combinations (+/- inhaled corticosteroids) via a single device or similar devices.
†Patients with ≥1 prescription (including prescription at index date) for both baseline and additional device prescribed at index date.

4.2 Study population

4.2.1 Inclusion criteria

Patients must meet the following inclusion criteria:

- Quality and Outcomes Framework (QOF) coded diagnosis for COPD ever recorded
- Aged ≥ 40 years at prescription date
- ≥ 2 years of continuous practice data
- ≥ 1 prescription for SABA, SAMA, LABA or LAMA as monotherapy or combinations (+/- ICS) via a single device or similar devices, prior to the prescription date
- ≥ 1 prescription for baseline device(s) **and additional** COPD therapy (LABA, LAMA, ICS or their combinations) via a separate inhaler device in the outcome period (including that at prescription date)

4.2.2 Exclusion criteria

Patients will be excluded from the analysis if they:

- Have ≥ 2 dissimilar devices prescribed prior to the prescription date
- Have ≥ 1 prescription for nebuliser prior to the prescription date

4.3 Study outcomes

The following study outcomes will be evaluated for patients in Phase 2 of the study:

4.3.1 Primary outcome

- Moderate and severe COPD exacerbation rate (sensitivity definition)*

4.3.2 Secondary outcomes

- Short-acting beta$_2$agonist (SABA) use*
- Adherence to COPD therapy*(exploratory)

4.4 Patient characterization

To assess baseline differences and identify potential confounders for the outcome analyses, patients will be characterised according to the following in the baseline period (for both matched and unmatched):

- Age
- Sex
- BMI
- Percent predicted FEV_1
- FEV/FVC ratio
- Smoking status
- Co-morbidities
- COPD exacerbations
- Lower respiratory tract infections
- Prior maintenance COPD therapy + doses
- COPD severity (risk and symptoms) defined by Global Initiative for Chronic Obstructive Lung Disease (GOLD) group (A, B, C, D)
- Lung function defined by GOLD stage (1, 2, 3, 4)

*Refer to definitions in Appendix

5.0 Analyses

5.1 Software

All analysis will be carried out using IBM SPSS Statistics version 22 [9], SAS version 9.3 [10] and Microsoft Office EXCEL 2013.

5.2 Significance testing

Statistically significant results will be defined as $p < 0.05$ and trends as $0.05 \leq p < 0.10$.

5.3 Analyses

Exploratory data analysis will be carried out for all outcome variables. Full details are given in section 7.4.

5.4 Exploratory data analysis

5.4.1 Summary statistics

Summary statistics will be produced for all baseline and outcome variables, as a complete dataset and by treatment groups. For variables measured on the interval or ratio scale, these included:

- Sample size (n)
- Percentage non-missing
- Mean
- Variance / Standard Deviation
- Range (Minimum / Maximum)
- Median
- Inter-quartile Range (25th and 75th percentiles)

For categorical variables, the summary statistics included:

- Sample size (n)
- Range (if applicable)
- Count and Percentage by category (distribution).

5.4.2 Plots

Plots will be produced for all baseline and outcome variables, as a complete dataset and by treatment group. For variables measured on the interval or ratio scale, these will include

- Frequency plots

- Box plots

Frequency plots will be used to illustrate the distribution of the variable and whether categorisation would be necessary (for example, if heavily skewed). Box plots will be used to illustrate the location and spread of the variable and identify potential outliers. Plots by treatment group will be used to highlight baseline and outcome differences between treatment groups.

For categorical variables, mosaic plots will be used to illustrate distributions and highlight baseline and outcome differences between treatment groups

5.4.3 Matching

Matching will be performed to provide a more robust analysis with matching criteria selected as appropriate and informed by cohort characterisation through a combination of categorical and continuous demographic and clinical variables. Any residual differences remaining after matching that are considered to be significant between the treatment arms, or predictive of outcomes, will be considered as potential confounders and will be adjusted for through conditional regression modelling.

Patients will be matched on key demographic and disease severity characteristics. The exact matching criteria will be defined following baseline cohort characterisation.

5.5 Outcomes analysis

Unadjusted outcomes will be compared using Chi-square tests for categorical or the Mann-whitney test for continuous data (for unmatched data) or conditional logistic regressions (for matched data). Results will be reported as n (%) of patients who, in the year after the prescription date:

- experienced none, 1 or 2+ moderate and severe exacerbations
- experienced none, 1 or 2+ severe exacerbations (hospitalisations)
- Average daily SABA dosage (µg/day) and adherence to therapy (refill rate %) will be categorised (high/medium/low) as appropriate to the data

Exacerbation rates in the outcome period will be compared between cohorts using conditional Poisson regression models to obtain estimates of relative exacerbation rates. Results will be reported as rate ratios (RR) with 95% confidence intervals (CI).

For average daily SABA dosage and adherence, the adjusted odds of being in a higher SABA/adherence category will be compared between (matched) cohorts using conditional ordinal logistic regression models. Good adherence will be defined as >80% [11].

RR (95% CI) will be reported both before and after having adjusted for baseline predictors/confounders, defined as:

- Residual baseline differences after matching (conditional logistic regression, $p<0.10$)
- Baseline variables predictive of the outcomes (full multivariable model, $p\leq0.05$)
- Potential confounders will be checked for co-linearity using Spearman's correlation coefficients for linear relationships ($\rho>0.3$), plots and univariate logistic regressions for non-linear relationships

6.0 Regulatory and ethical compliance

This study was designed and shall be implemented and reported in accordance with the criteria of the "European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study" and follows the ENCePP Code of Conduct (EMA 2014). Once a final version of the protocol has been agreed and reviewed by the advisory group, this study will be registered with www.encepp.eu.

7.0 Data dissemination

Initial results will be presented in poster and/or oral format at appropriate thoracic conferences. A manuscript containing more detailed results and methodology will be submitted to a journal specialising in respiratory medicine.

8.0 Advisory group

Steering Committee:

- SinthiaBosnic-Anticevich
- Henry Chrystyn
- Richard Costello
- Myrna Dolovich
- Monica Fletcher
- Federico Lavorini
- Roberto Rodríguez-Roisin
- Dermot Ryan
- David Price

9.0 Research team

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10.0 Timelines

Table 1. Study timeline

Action	Due date
Protocol	28th August
Data extraction	2 weeks
Unmatched baselines	4 weeks
Matching	2 weeks
Matched baseline analysis	4 weeks
Outcomes and statistics (adjusted analyses)	4 weeks
Report/slide set	4 weeks
Manuscript	6-8 weeks from final report

11.0 References

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12.0 APPENDIX : defnitions

12.1 Body MASS Index (BMI)

The **Body Mass Index** is a representative measure of body weight based on the weight and height of the subject. It is defined as the weight (in kg) divided by the square of the height (in m) and is measured in kg/m^2.

BMI categories:

Underweight	<18.5 kg/m^2
Normal	18.5 kg/m^2 - 24.99 kg/m^2
Overweight	25 kg/m^2 - 29.99 kg/m^2
Obese	≥30 kg/m^2

12.2 Charlson Comorbidity Index (CCI)

The **Charlson Comorbidity Index** was developed in the US in 1987 as a method of classifying prognostic comorbidity in longitudinal studies [8]. It predicts the one-year mortality for a patient who may have a range of comorbid conditions such as heart disease, AIDS or cancer. Each condition is assigned a "weight" depending on the risk of dying associated with the condition; scores are then summed to give a total score predicting mortality.

The weights were revised and up-dated (for example, mortality due to HIV has fallen) by Dr. Foster Intelligence (DFI) in their HSMR Methodology documentation [9] and calibrated using UK data (due to differences in coding practice and hospital patient population characteristics from the US), using ICD-10 codes. As a result:

- DFI have expanded the coding definition of some conditions;
- Only secondary diagnoses (DIAG02 - DIAG14) are now considered;
- There is greater variation in weights between conditions and the Charlson Index (the sum of the weights) can be treated as a continuous variable (limited to the range 0 - 50) for the purposes of risk adjustment.

The weights, codes and conditions used in this study are summarised in the following table:

Condition	Condition Name	ICD - 10 codes	New weight
1	Acute myocardial infarction	I21, I22, I23, I252, I258	5
2	Cerebral vascular accident	G450, G451, G452, G454, G458, G459, G46, I60 - I69	11
3	Congestive heart failure	I50	13
4	Connective tissue disorder	M05, M060, M063, M069, M32, M332, M34, M353	4
5	Dementia	F00, F01, F02, F03, F051	14
6	Diabetes	E101, E105, E106, E108, E109, E111, E115, E116, E118, E119, E131, E131, E136, E138, E139, E141, E145, E146, E148, E149	3
7	Liver disease	K702, K703, K717, K73, K74	8
8	Peptic ulcer	K25, K26, K27, K28	9
9	Peripheral vascular disease	I71, I739, I790, R02, Z958, Z959	6
10	Pulmonary disease	J40 - J47, J60 - J67	4
11	Cancer	C00 - C76, C80 - C97	8
12	Diabetes complications	E102, E103, E104, E107, E112, E113, E114, E117, E132, E133, E134, E137, E142, E143, E144, E147	- 1
13	Paraplegia	G041, G81, G820, G821, G822	1
14	Renal disease	I12, I13, N01, N03, N052 - N056, N072 - N074, N18, N19, N25	10
15	Metastatic cancer	C77, C78, C79	14
16	Severe liver disease	K721, K729, K766, K767	18
17	HIV	B20, B21, B22, B23, B24	2

Table 2: Co morbid conditions and scores used in the Charlson Comorbidity Index (CCI)

12.3 Moderate/severe COPD exacerbations (sensitivity definition)

An exacerbation is defined as an occurrence[*] of the following:

1. COPD-related:[†] Unscheduled hospital admission / A&E attendance; OR
2. An acute[‡] course of oral steroids with lower respiratory consultation;[§] OR
3. Antibiotics prescribed with lower respiratory consultation[§]

12.4 SABA usage

Average daily SABA dosage during outcome (and baseline) year, calculated as average number of puffs per day over the year multiplied by strength (in µg);

i.e. $$\frac{\text{Number of inhalers} * \text{doses per inhaler}}{365} * \text{strength}$$

and categorised as appropriate to the data.

[*]Where ≥1 oral steroid course / hospitalisation / antibiotics prescription occur within 2 weeks of each other, these events will be considered to be the result of the same exacerbation (and will only be counted once).

[†]**COPD-related Hospitalisations:** consist of either a definite COPD Emergency Attendance or a definite COPD Hospital Admission; OR a generic hospitalisation Read code which has been recorded on the same day as a **Lower Respiratory Consultation**[d] (see below; (a) – (c) only and excluding where the only lower respiratory code recorded on that day was for a lung function test).

[‡]Acute oral steroid use associated with COPD exacerbation treatment will be defined as:

- All courses that are definitely not maintenance therapy, and/or
- All courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed), and/or
- All courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions.

where "maintenance therapy" is defined as: daily dosing instructions of ≤10mg Prednisolone or prescriptions for 1mg or 2.5mg Prednisolone tablets where daily dosing instructions are not available.

[§]**Lower Respiratory Consultations -** consist of the following:
a) Lower Respiratory Read codes (including Asthma, COPD and LRTI Read codes);
b)Asthma/COPD review codes excluding any monitoring letter codes;
c)Lung function and/or asthma monitoring
d)Any additional respiratory examinations, referrals, chest x-rays, or events.

12.5 Therapy adherence rate

Based on therapy prescription rates:

12.5.1 Adherence over 1 year

Number of days per pack = Number of actuations per pack / Number of actuations per day

Total Pack Days = Σ (Number days per pack)

Refill Rate % = (Total pack days/365) * 100

Note: when inhaler duration is very different between two treatment groups, adherence may be a biased outcome – thus adherence will be considered carefully at the patient matching stage.