Study protocol

Effectiveness of prescribing comparable vs. non-comparable devices for COPD management

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

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TITLE	Effectiveness of prescribing comparable vs. non-comparable devices for COPD management
Subtitle	A historical cohort, UK database study comparing disease outcomes and adherence in patients with COPD prescribed comparable inhaler devices (in terms of inhalation technique) vs those prescribed non-comparable devices
Protocol version number	3
Study aims and objectives	Given that patients with COPD are often prescribed more than one inhaler device, the following study aims to investigate whether the use of non-comparable 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.
Country of study	United Kingdom
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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 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, when correct inhaler use is fundamental for effective disease management [3].

Patients with COPD are often prescribed more than one inhaler device (e.g. for bronchodilator and ICS), 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], the following 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 non-comparable inhaler devices, in terms of inhalation technique, versus comparable devices

2.0 Study aims and objectives

2.1 Study aims

Given that patients with COPD are often prescribed more than one inhaler device, the following study aims to investigate whether the use of non-comparable 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 2 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 comparable vs non-comparable devices
  - Compare the effectiveness (in terms of moderate and severe exacerbation prevention) of prescribing inhaler devices with comparable inhalation techniques vs prescribing devices with non-comparable inhalation techniques in patients with COPD
  - Assess therapy adherence in patients with COPD prescribed inhaler devices with comparable inhalation techniques* vs patients prescribed devices with non-comparable inhalation techniques

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

3.0 Data source

For both phase 1 and phase 2:

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.

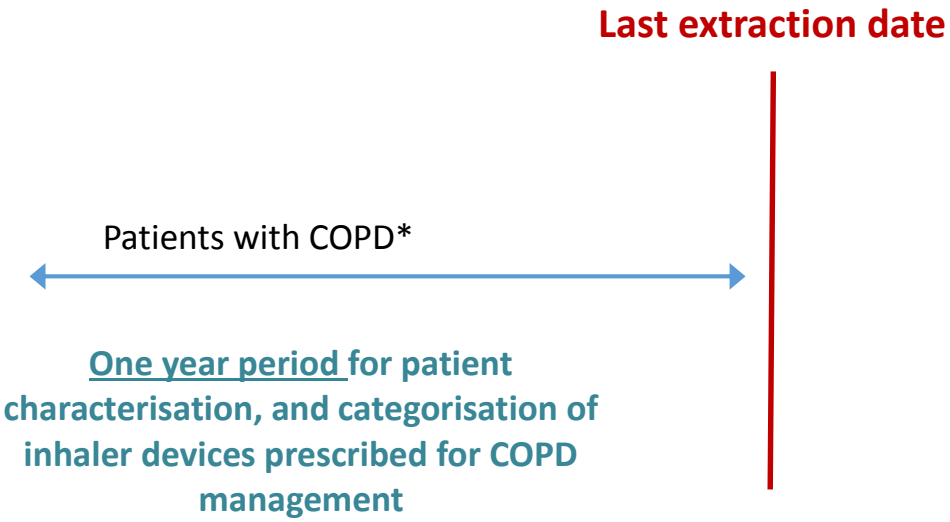
4.0 Phase 1

4.1 Study design

This is a historical cohort, UK database study that will review inhaler device prescription patterns and categorisation of devices (based on required inhalation technique) commonly prescribed for COPD management.

4.2 Study period

The study period for **Phase 1** will be the last year of data in OPCRD, i.e. a 12-month period.



4.3 Study population

4.3.1 Inclusion criteria

Patients must meet the following inclusion criteria:

- Quality and Outcomes Framework (QOF) coded diagnosis for COPD ever recorded
- Aged ≥ 40 years at start of study year
- ≥ 2 different inhaled treatments

*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 comparable devices.

4.3.2 Exclusion criteria

- No patients will be excluded from this part of the analysis

4.4 Study objectives

Phase 1 of the study will involve a categorisation (based on required inhalation technique) and descriptive summary of commonly prescribed devices for COPD management.

- List of inhaler devices prescribed for COPD management in a UK patient population, describing for each device:
  - Therapies available (short and long-acting bronchodilators, inhaled corticosteroids and fixed dose combinations)
  - Proportion of different devices per treatment regimen

- Categorisation of inhaler devices based on similarities in required inhalation speed and strength for correct use (i.e. groups of comparable devices)*
- Patterns of inhaler device prescriptions, focusing on co-prescriptions for comparable and non-comparable devices

Preliminary table of devices categorised by inhalation technique (i.e. groups of comparable devices; to be further populated using OPCRD data):

Aerosols				**Single-dose capsule DPIs**		**Multi-dose DPIs**		
Manual-actuated MDI	Manual-actuated MDI + spacer	Breath-actuated MDI	Soft mist inhaler	Low resistance	High resistance	Medium resistance	Medium high resistance	High resistance
pMDI	‘’ +spacer	Autohaler	Respimat	Breezehaler	Handihaler	Accuhaler (Diskus)	Turbohaler	Twisthaler
		Easi-Breathe		Aerolizer		Novolizer	Clickhaler	Easyhaler
						Genuair	Pulvinal	
						Elipta		

*Based on expert advice

5.0 Analyses

5.1 Software

All analysis will be carried out using IBM SPSS Statistics version 22 [12], SAS version 9.3 [13] and Microsoft Office EXCEL 2013.

5.2 Significance testing

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

6.0 Descriptive analyses

6.1 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:

- Age
- Sex
- BMI
- Percent predicted FEV_1
- Smoking status
- Co-morbidities
- COPD exacerbations
- 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)

7.0 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.

8.0 Data dissemination

Initial results will be first presented and discussed at the DASG meeting in May 2015, and followed shortly after with presentations 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.

9.0 Advisory group

Steering Committee:

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

10.0 Research team

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11.0 Timelines

Table 1. Study timeline

Action	Timeline
Protocol (phase 1 and 2*)	1 week
Data extraction (phase 1)	2 weeks
Descriptive analysis (phase 1)	4 weeks
Report/slide set (phase 1) (*to be presented at the 20 May 2015 DASG meeting*)	4 weeks
Update of protocol (phase 2*)	1 week
Data extraction (phase 2)	2 weeks
Statistical analyses (phase 2)	3 weeks
Report/slide set (phase 2)	4 weeks
Manuscript	6-8 weeks from final report

*Phase 2 may be updated following phase 1

12.0 References

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13.0 APPENDIX : defnitions

13.1 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

13.2 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)

13.3 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§

13.4 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.

13.5 Therapy adherence rate

Based on therapy prescription rates:

13.5.1 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.