Study protocol

Real-life effectiveness evaluation of budesonide/formoterol (BF) Spiromax® for the management of asthma and COPD

Four complimentary post-marketing retrospective, observational studies to evaluate the real-life effectiveness and cost effectiveness of BF Spiromax and to characterise patients prescribed BF Spiromax in the two years following product launch in the United Kingdom

Date:
15 September 2015

Teva contacts:
Hicham Benhaddi

Research in Real-Life

Research in Real-Life Pte Ltd
16 Raffles Quay
#33-03 Hong Leong Building
Singapore
048581

Research in Real-Life Ltd
5a Coles Lane
Oakington
Cambridge CB24 3BA
United Kingdom

Phone +44 1223 967874
Fax (+44) 0808 2800 792
Email: bakhtiyor@rirl.org
Web site http://www.rirl.org

Chief Investigator:

Professor David Price, Professor of Primary Care Respiratory Medicine and RiRL Director
Mobile: +44 7787905057
Office number: +44 2081233923
Skype ID: respiratoryresearch
Email: david@rirl.org

Project coordinator:

Bakhtiyor Khalikulov
Research in Real-Life Ltd
5a Coles Lane, Oakington, Cambridgeshire CB24 3BA, UK
Direct number: +44 1223 967874
Email: bakhtiyor@rirl.org

Study sponsor:

Teva Pharmaceutical Industries Ltd.

Primary contact

Hicham Benhaddi (Hicham.Benhaddi@tevaeu.com)

TITLE	Real-life effectiveness evaluation of budesonide/formoterol (BF) Spiromax® for the management of asthma and COPD
Subtitle	Four complimentary post-marketing studies to evaluate the real-life effectiveness and cost effectiveness of BF Spiromax® and to characterise patients prescribed BF Spiromax® following product launch in the United Kingdom
Protocol version number	3.0
Medicinal product	- Budesonide/formoterol fumarate dihydrate (DuoResp® Spiromax®) 160/4.5, 320/9 µg DPI. - Budesonide/formoterol fumarate dihydrate (Symbicort® Turbohaler®) 100/6, 200/6, 400/12 µg DPI. - Salmeterol/fluticasone (Seretide® Accuhaler®) 50/100, 50/250, 50/500 µg DPI.
Product code	BF Spiromax (231-10-01349; 231-10-01352)
Marketing authorisation holder	Teva Pharma B.V. Computerweg 10, 3542 DR Utrecht The Netherlands
Marketing authorisation number	N/A
Study aims and objectives	- (1) To characterise patients changing to DuoResp® Spiromax® from other licensed FDC inhalers. - To investigate (2) acceptability of the change by patients, (3) effectiveness for improving asthma / COPD outcomes and (4) it's cost-effectiveness.
Country of study	United Kingdom
Author / Research lead	Bakhtiyor Khalikulov RiRL UK Ltd 5a Coles Lane Oakington Cambridge CB24 3BA United Kingdom

Contents

1.0 Background

Asthma and chronic obstructive pulmonary disease (COPD) are major non-communicable diseases associated with high morbidity, mortality and socio-economic costs.[1,2]

Asthma affects 300 million people worldwide and causes approximately 250,000 deaths annually and 15 million disability-adjusted life years (WHO, GINA).[3,4] COPD has a comparatively lower prevalence affecting 64 million people, but a ten times higher mortality reaching more than 3 million people causing 6% of all deaths globally (WHO, 2015).[5,6] Available estimations project that asthma and COPD will affect an additional 100 million people and become the third leading cause of death by 2030.[2,6,9]

The UK has one of the highest prevalences of asthma and COPD globally. The prevalence of COPD is estimated as 13% in the population aged over 35 and it accounts for 25,000 deaths a year.[7,8] The prevalence of asthma in the UK is about 16% and it affects approximately 3 - 5.4 million people in the UK causing 1,200 – 1,500 deaths per year [5,6,7,53] Therefore, effective management of asthma and COPD becomes an important task in clinical and primary care in the UK.

Delivery of drugs by inhalation is a fundamental element of the modern management of asthma and COPD. It allows rapid delivery of drugs to the lungs in comparatively small doses. Different types of licensed inhalers have specific advantages and disadvantages connected with inhaler technique and cost, but demonstrate similar clinical effectiveness in Randomized Clinical Trials where inhalers are predominantly used correctly over a relatively short period of time.[10,11] However, the effectiveness of inhalers in real-world practice may vary, increasing the importance of the correct choice of inhaler for optimal treatment of patients.[12]

Globally, pressurised metered dose inhalers (pMDI) are the most frequently prescribed and cheapest devices.[12] At the same time many patients fail to use pMDI correctly because good coordination between inspiration and actuation is required to ensure correct inhalation and deposition of drug in the lung.[12,13,18,20,21]

A number of studies show that pMDIs are frequently misused. A study in France reported that 71% of patients misused pMDI's.[14] A nationwide study in Spain among 1,640 volunteers (746 patients, 466 nurses and 428 physicians) found that only 9% of patients, 15% of nurses and 28% of physicians showed a correct inhalation technique.[15] Moreover, existing evidence suggests that

patients who establish correct inhalation technique demonstrate incorrect pMDI use in the longer time periods.[16] Crompton and others confirmed these findings in longitudinal studies conducted between 1982 and 2000.[17-19] Clinical and observational studies report that poor pMDI inhalation technique results in suboptimal treatment response.[12,14,19]

Even with the correct inhalation technique, pMDIs are inefficient, especially the older types. They often deliver less than one third of the emitted dose to the lungs[34,35] and less than half of the emitted dose to the peripheral airways compared with DPIs.[34,36] The high proportion of drug deposit in the mouth and oropharynx can cause local as well as systemic side effects due to rapid absorption.[34,37,38] Change in the propellant and actuation in pMDIs led to improvements in lung deposition. Also, patients frequently fail to detect when the inhaler is empty and continue to use it when it may no longer be delivering the required dose.

Other types of inhalers such as dry powder inhalers (DPIs) have become available for asthma and COPD therapy. DPIs are more convenient to use because they don't require coordination of inhaler actuation and inhalation and overcome many of the problems inherent in pMDI design. DPIs have dose counters or inhalation control mechanisms and they don't use propellant gases and dispersants that may cause cough, throat irritation and occasionally paradoxical bronchoconstriction.[40]

Despite technical improvement, studies suggest that up to 94% of patients, depending on the DPI type and method of assessment, do not use their inhalers correctly that may lead to insufficient lung deposition.[24] The most frequent error when using DPIs is failure to exhale before inhalation.[24,25] Additionally, exhaling over a DPI cause excess moisture which decreases the next dose delivery.[26]

DPI performance mainly depends on the patient's inspiratory flow and the turbulence level within the device.[23] With DPIs, the size of emitted particles and consequently drug deposition are dependent on inspiratory flow rate achieved by the patient.[12] Patients should inhale maximally at the beginning of the inhalation manoeuvre. However, if patients start too slowly, then the size of the emitted particles increases. Most of these particles will be too large to inspire and are deposited in the mouth and oropharynx.[12] This is an important limitation in therapy success for patients unable to generate sufficient inspiratory airflow.[27] Up to 39% and 66% of patients, aged 18-59 and 60-99 years respectively, demonstrated insufficient inspiratory flow in a study of the inhalation technique in patients with respiratory diseases.[8]

One study from 2001 systematically reviewed the evidence from clinical trials evaluating the clinical effectiveness of different inhaler devices in the delivery of inhaled corticosteroids and beta2-bronchodilators for patients with asthma and COPD, including chlorofluorocarbons (CFC)-free inhaler devices using hydrofluoroalkanes (HFAs), breath-actuated pMDIs (BA-pMDI).[10] They concluded that no difference was demonstrated in clinical effectiveness between nebulisers and alternative inhaler devices compared to standard pMDI with or without a spacer device. Thus, interchangeability of DPIs is an area of interest that needs to be addressed in the future studies.[30,31]

DuoResp Spiromax® is a novel product delivered via Teva's proprietary DPI. It is a combination of budesonide and formoterol [BF] for the management of asthma and COPD in adults (≥18 years old) where use of an inhaled corticosteroid (ICS) /long-acting β_2 agonist (LABA) is appropriate.[29,32] Teva received European Marketing Authorisation for this product in April 2014 and the product was launched in the UK in September 2014.[33]

DuoResp Spiromax® is indicated in the regular treatment of asthma in patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β2 adrenoceptor agonists. As well as in patients already adequately controlled on both inhaled corticosteroids and long-acting β2 adrenoceptor agonists.[42] Also, DuoResp Spiromax® is recommended for symptomatic treatment of patients with severe COPD (FEV1 < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.[42]

DuoResp Spiromax® was developed to maximise user-friendliness to improve treatment adherence and clinical outcomes.[45,46,47] The device provides patients with confirmation by taste (lactose) that a dose has been successfully administered, and a single-increment dose counter provides further means of monitoring therapy.[48]

Pharmacokinetic equivalence of BF Spiromax to BF Turbohaler was demonstrated in comparative studies.[49,50] Arp and colleagues reported consistency of delivered dose of BF *via* DuoResp® Spiromax® in the laboratory and under simulated 'real-world' conditions.[51]

Evidence on DuoResp® Spiromax® safety and efficacy so far has mainly been gathered from randomised clinical trials with strict inclusion and exclusion criteria and predominantly correct inhalation technique.[12] Though, effectiveness of new DPI formulations in the real-world settings

might be influenced by additional factors such as device characteristics and inhaler technique that could be addressed in the future studies.

Further longitudinal studies with DuoResp Spiromax® will ascertain effectiveness in real-life clinical practice. Indeed, historical cohort studies using electronic data from GP practices will enable investigation of real-world outcomes.

Four studies utilising clinical practice data from the two years following DuoResp Spiromax® launch would enable multiple assessments of (1) the characteristics of patients changing to DuoResp Spiromax®, (2) the acceptability of change by patients, (3) the real-world effectiveness and (4) the cost effectiveness of DuoResp Spiromax®.

2.0 Study aims and objectives

This study will consist of four complimentary post-marketing studies aiming to characterise patients who change to DuoResp Spiromax® from another ICS/LABA FDC and evaluate the acceptability, and the real-life effectiveness and cost-effectiveness of DuoResp Spiromax®. Each phase of the study has its own specific aims and objectives.

Phase 1

2.1. Aim

To characterise patients changing to DuoResp Spiromax® from other licensed FDCs of inhaled corticosteroids (ICS) and LABA and describe prescription patterns prior to this change in patients with asthma and COPD.

2.1.2 Objectives

1. To characterise patients who change to DuoResp Spiromax® from other ICS/LABA FDCs, during the one-year period prior to switching, considering demographics, comorbidities and markers of asthma/COPD disease severity and control.
2. To evaluate prescription patterns and the history of medications indicated for use in both asthma and COPD issued during the one-year baseline period prior to the patients' switching to DuoResp Spiromax® including: respiratory therapies prescribed, types of inhalers, dosage/variation of medication.

Phase 2

2.2 Aim

To determine the acceptability of change to DuoResp Spiromax® from Symbicort Turbuhaler or Seretide Diskus in patients during a six-month outcome period.

2.2.1 Objective

To evaluate persistence of change to DuoResp Spiromax® by patients during the six-month outcome period after switching to DuoResp Spiromax®. A "change-back" rate of >17% will be considered as potentially indicative of dissatisfaction with change.

Phase 3

2.3 Aim

To evaluate whether disease control, healthcare resource utilisation and costs are non-inferior or improve after a change to DuoResp® Spiromax® within patients by comparing the patients'

asthma and COPD outcomes and related costs before and after their change to DuoResp® Spiromax® from other ICS/LABA FDCs.[1]

2.3.1 Objectives

1. To evaluate whether DuoResp Spiromax® is non-inferior to the patients' baseline therapy in terms of achieving Risk Domain Control[2]. This would be based on a non-inferiority limit of 10% reduction in Risk Domain Control.
2. To analyse the change in asthma or COPD related exacerbation rate, hospitalisations and change in treatment stability before and after change from Symbicort Turbuhaler or Seretide Diskus to DuoResp Spiromax®.
3. To compare healhcare utilization and related costs before and after change to DuoResp Spiromax® in terms of respiratory drug prescriptions, primary care consultations and respiratory related hospital costs.

Phase 4

2.4 Aim

To evaluate whether the level of disease control, ,healthcare resource utilisation and costs is non-inferior or superior in patients who have changed to DuoResp Spiromax® from other ICS/LABA FDCs compared with patients who continue this use. Patients will be matched on key baseline differences identified in phase 2.

2.4.1 Objectives

1. To analyse whether DuoResp® Spiromax®is non-inferior or superior to other ICS/LABA FDCs in terms of achieving disease control in asthma and COPD during the outcome period in the two matched cohorts:
   A. Patients changing from other ICS/LABA FDCs to DuoResp® Spiromax®.
   B. Patients continuing treatment with their initiation ICS/LABA FDCs.
   Non-inferiority would be based on a non-inferiority limit of 10% reduction in disease control.
2. To compare exacerbation rates, hospitalisations, change in treatment stability and cost of the therapy in relation to asthma and COPD outcomes between the two matched cohorts described above.

[1] The ICS/LABA FDC therapy to be included in the comparator arm can be decided following phase 1, where prescribing practice will be evaluated.

[2] Risk Domain Control defined as absence of: exacerbations, unplanned asthma or COPD-related outpatient appointments, and antibiotics with evidence of respiratory review.

3.0 Phase 1

3.1 Study design

Historical cohort database study characterising patients with asthma or COPD who changed to DuoResp® Spiromax® from other licensed FDCs of ICS + LABA. Patients with a minimum of one year data prior to the date that they receive their first DuoResp® Spiromax® prescription will be included in this phase.

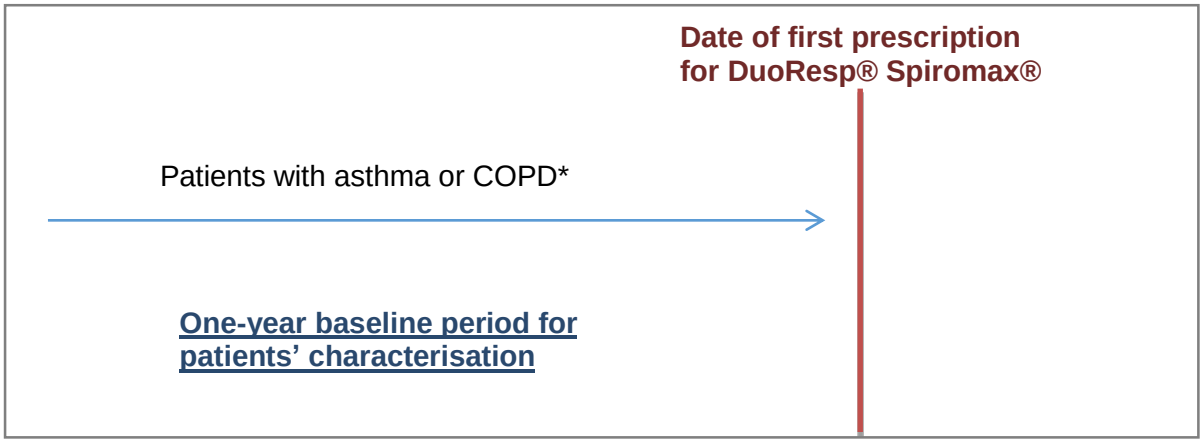

Figure 1: Study design for Phase 1.

3.2 Study population

3.2.1 Inclusion and exclusion criteria

Inclusion criteria
Asthma patients: • Aged ≥18 years at first prescription for DuoResp® Spiromax® • Evidence of asthma, defined as a diagnostic code and/or ≥2 prescriptions for asthma therapy[3] during the baseline year
COPD patients: • Aged ≥40 years at first prescription for DuoResp® Spiromax® • A diagnostic Read code for COPD qualifying for the inclusion in the register of patients with COPD, which GP practices in the UK maintain for the Quality Outcomes Framework. This requires a post-bronchodilator FEV_1/FVC <0.70
Evidence of at least 3 prescriptions for ICS/LABA FDC therapy during the baseline period
One year of continuous practice data prior to their first prescription for DuoResp® Spiromax®
Exclusion criteria
Prescribed DuoResp® Spiromax® outside of the licensing conditions Diagnosis for any chronic respiratory disease diagnosis, except asthma, at any time (for asthma patients)

[3] Includes prescriptions for bronchodilators including beta2-agonists, anticholinergics, theophylline or combination therapy, inhaled corticosteroids, combination inhaled corticosteroids and bronchodilator therapy

3.3 Data source

The study will use patient data from the Optimum Patient Care Research Database (OPCRD). The study team work with fully anonymised data, removed of any patient identifiable information. The OPCRD is developed, maintained, and owned by Optimum Patient Care, a social enterprise company that aims to improve patient outcomes through medical research and services. OPC provides evidence-based recommendations to UK general practices through bespoke software and practice reports.

The OPCRD currently comprises longitudinal medical records for over 2.2 million patients from over 550 primary care practices across the UK. The OPCRD contains two types of data: (1) routinely recorded clinical data and (2) questionnaire responses from over 40,000 patients with respiratory conditions. The OPC questionnaires are a compilation of validated questions covering symptoms, disease control, triggers, side effects, quality of life, and unique adherence measures. Indeed the OPCRD is the only database in the UK that complements routinely recorded disease coding and prescribing information with patient-reported outcomes. The OPCRD also links with nationwide practice prescribing data to enable targeted delivery of dataset needs.

The database has received a favourable opinion from the Health Research Authority for clinical research use (REC reference: 15/EM/0150). Governance is provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG)[43] to govern the standard of research conducted on internationally recognised databases. All research using OPCRD will be registered on established study databases such as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)[44].

3.4 Study variables

Patients changing to DuoResp® Spiromax® from other licenced FDC LABA-ICS DPI therapies will be characterised including, but not limited to, the demographics, comorbidities, asthma/COPD disease severity and control, respiratory-related clinical and prescribed therapy variables recorded by a general practitioner at/closest or during the year prior to the date of their first DuoResp® Spiromax® prescription.

3.4.1 Demographics

- Age and gender (at the time of the clinical review)

- Body Mass Index (BMI), closest to the index date: defined as the ratio of weight (kg) to squared height (m^2), and categorised as 'underweight' (< 18.5 kg/m^2), 'normal weight' (≥ 18.5 kg/m^2 and < 25 kg/m^2), 'overweight' (≥ 25 kg/m^2 and < 30 kg/m^2) and 'obese' (≥ 30 kg/m^2)
- Smoking status, closest to the index date: non-smoker, current smoker and ex-smoker

3.4.2 Comorbidities

Comorbidities of interest will include:

- Asthma for COPD cohort (ACOS)*
- Ischaemic heart disease*
- Heart failure*
- Diabetes*
- Pneumonia*
- Gastro-oesophageal reflux disease (GERD)**
- Allergic and non-allergic rhinitis**
- Other chronic lung diseases*
- Charlson comorbidity index score[4] (CCI) score - a weighted index that takes into account the number and seriousness of comorbid diseases to estimate the risk of death from comorbid diseases[52]

3.4.3 Lung function

- Forced Expiratory Flow in one second (FEV_1), closest to the index prescription date (IPD): refers to the forced expiratory volume in one second, expressed as a percentage of the predicted normal value
- Peak Expiratory Flow (PEF), closest to IPD: refers to the the maximum flow at the outset of forced expiration

[4]Based on the International Classification of Diseases, 9th revision (ICD-9) predicts the ten-year mortality for patients with comorbidities, where each comorbidity is assigned a score.

* with a diagnostic code recorded at any time prior to or at the last extraction date

** with a diagnostic code recorded + treatment course at any time prior to or at the last extraction date

- FEV_1/ Forced Vital Capacity (FVC) ratio, closest to IPD: represents the proportion of a person's vital capacity that they are able to expire in the first second of forced expiration

3.4.4 Disease severity and control

COPD patients:

- GOLD group, closest to the index date: based on 2014 GOLD guidelines:[9]
  - A = low risk, less symptoms: mMRC of ≤ 1; and FEV_1 ≥ 50% and/or ≤ 1 exacerbation per year (with no hospitalisations for exacerbations)
  - B = low risk, more symptoms: mMRC of ≥ 2; and FEV_1 ≥ 50% and/or ≤ 1 exacerbation per year (with no hospitalisations for exacerbations)
  - C = high risk, less symptoms: mMRC of ≤ 1; and FEV_1 < 50% and/or ≥ 2 exacerbations per year (or ≥ 1 hospitalisation for exacerbation)
  - D = high risk, more symptoms: mMRC of ≥ 2; and FEV_1 < 50% and/or ≥ 2 exacerbations per year (or ≥ 1 hospitalisation for exacerbation)
- Moderate/severe COPD exacerbations, defined as the occurrence of any of the following:[5]
  - Acute course of oral corticosteroids[6]
  - Antibiotics prescribed with a lower respiratory consultation[7]
  - COPD-related, unscheduled hospital admission / emergency department attendance (i.e. severe exacerbation)[8]

[5] Where > 1 oral corticosteroid courses / hospitalisations / antibiotic prescriptions occurred within 2 weeks of each other, they will be considered to be the result of the same exacerbation (and only counted once).

[6] Defined as any of the following: (a) courses that are definitely not maintenance therapy (defined as prescriptions for Prednisolone with daily dosing instructions of ≤ 10 mg, and for 1 mg or 2.5 mg Prednisolone tablets where daily dosing instructions are not available); (b) courses where dosing instructions suggest exacerbation treatment (e.g. 6-1 reducing, or 30 mg as directed); and (c) courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions.

[7] Identified by Read codes for any of the following: (a) lower respiratory diagnosis (including asthma, COPD and lower respiratory tract infection codes); (b) asthma/COPD review codes excluding any monitoring letter codes; (c) lung function and/or asthma monitoring codes; and (d) any additional respiratory examinations, referrals, chest x-rays, or events.

[8] Identified by Read codes for any of the following: (a) definite COPD emergency attendance or definite COPD hospital admission; (b) generic hospitalisation code which has been recorded on the same day as a lower respiratory consultation (see footnote above, refers to (a) - (c) only and excluding those where the lower respiratory code was for a lung function test only).

- mMRC score, closest to the index date: refers to the modified British Medical Research Council questionnaire for assessing the severity of breathlessness, graded from 0, lowest score of breathlessness, to 4, highest score of breathlessness.[9] Both routine medical practice recorded and patient questionnaire mMRC scores will be used, with the most recent score taking precedence

- CAT score, based on COPD Assessment Test (where available)

Asthma patients

- GINA steps of treatment 1-5, closest to the index date (based on GINA guidelines 2014

- GINA control, closest to the index date (based on GINA guidelines 2014)

    - Step 1. Symptoms <once weekly; brief exacerbaitons; nocturnal symptoms ≤twice monthly; PEF or FEV_1 variability <20%

    - Step 2. Symptoms >once weekly but <once daily; exacerbaitons may affect activity and sleep; nocturnal symptoms >twice monthly; PEF or FEV_1 variability 20-30%

    - Step 3. Symptoms daily; exacerbaitons may affect activity and sleep; nocturnal symptoms >once weekly; PEF or FEV_1 variability >30%

    - Step 4. Symptoms daily; frequent exacerbaitons; frequent nocturnal asthma symptoms; limitations of physical activities; PEF or FEV_1 variability >30%

- Severe asthma exacerbation event based on the ATS/ERS Position Statement is defined as an occurrence[9] of asthma related
    - Hospital admissions. Asthma-Related Hospitalisations: consists of either a definite Asthma Emergency Attendance or a definite Asthma Hospital Admission; OR a generic hospitalisation Read code which has been recorded on the same day as a Lower Respiratory Consultation (see below; (a) – (c) only and excluding where the only lower respiratory code recorded on that day was for a lung function test) OR

    - A&E attendance, OR

    - Acute course of oral corticosteroids 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

[9] Where ≥1 oral corticosteroid course / hospitalisation occurs 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).

all courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions; “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.

- Acute respiratory event is defined as an occurrence of the following:
    a. Asthma-related hospital admission OR
    b. A&E attendance, OR
    c. An acute course of oral steroids; OR
    d. Antibiotics prescribed with lower respiratory consultation

- Risk Domain Asthma Control (RDAC)
  Controlled asthma is defined as the absence of the following aspects of asthma risk during the outcome year:
    a. Asthma-related hospital admission AND A&E attendance, AND out-patient department attendance
    b. Acute course of oral corticosteroids with evidence of a lower respiratory consultation

3.4.5 Prescriptions

- Respiratory-related therapies, in the year prior to the index date:
    - Short-acting β_2 agonist (SABA) and/or short-acting muscarinic antagonist (SAMA)
    - Long-acting β_2 agonist (LABA)
    - Long-acting muscarinic antagonist (LAMA)
    - Inhaled corticosteroids (ICS)
    - Fixed combinations of LABA and ICS
    - LeukoTriene Receptor Antagonists LTRA

  SABA reliever usage, in the year prior to the index date: average daily dose in µg/day calculated as

  ([Count of inhalers x doses in pack] / 365) x µg strength

3.5 Statistical analysis

3.5.1 Software used

Statistical analysis will be performed using SPSS Statistics version 23 software (IBM SPSS Statistics, Feltham, Middlesex, United Kingdom) and SAS version 9.3 software (SAS Institute, Marlow, Buckinghamshire, United Kingdom).

3.5.2 Baseline characterisation

Data will be prepared for analysis by investigating outliers, type and reason for missing data, and categorising skewed data if appropriate. Summary statistics will be produced for all baseline variables. Results will be reported as:

- Variables measured on the interval or ratio scale: sample size (n) and percentage of non-missing data; mean (standard deviation) and median and inter-quartile range (25^{th} and 75^{th} percentiles)
- Categorical variables: sample size (n); count (n) and percentage (%) by category (distribution)

4.0 Phase 2

4.1 Study design

Historical cohort database study involving patients who change their FDC therapy to DuoResp® Spiromax® from Symbicort® Turbohaler® / Seretide® Accuhaler®.[10] Patients with a minimum of one year data prior to (baseline) and six months of data post (outcome) the date that they receive their first DuoResp® Spiromax® prescription will be included in the study.

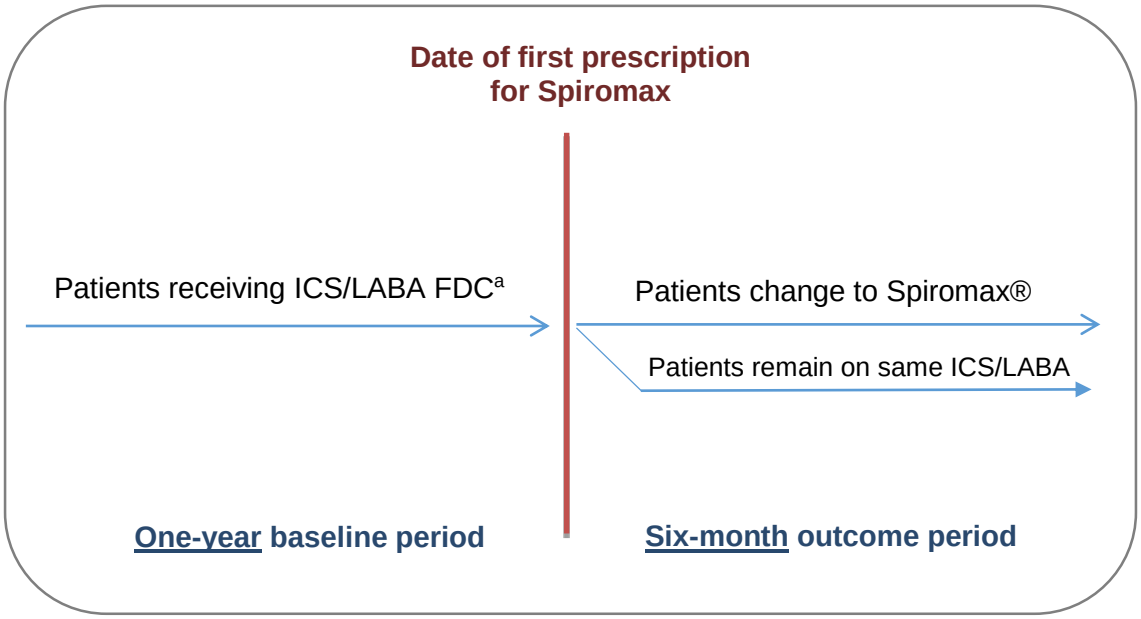

Figure 2: Study design for Phase 2.

4.2 Study population

4.2.1 Inclusion and exclusion criteria

Inclusion criteria
Asthma patients: • Aged ≥18 years at first prescription for DuoResp® Spiromax® • Evidence of asthma, defined as adiagnostic code and/or ≥2 prescriptions for asthma therapy[11] during the baseline year
COPD patients: • Aged ≥40 years at first prescription for DuoResp® Spiromax®

[10] The ICS/LABA FDC therapy to be included in the comparator arm can be decided following phase 1, where prescribing practice will be evaluated

[11] Includes prescriptions for bronchodilators including beta2-agonists, anticholinergics, theophylline or combination therapy, inhaled corticosteroids, combination inhaled corticosteroids and bronchodilator therapy

• A diagnostic Read code for COPD qualifying for the inclusion in the register of patients with COPD, which GP practices in the UK maintain for the Quality Outcomes Framework. This requires a post-bronchodilator FEV_1/FVC <0.70
Evidence of at least 3 prescription for ICS/LABA FDC therapy during the baseline period
Continuous study period comprising of a minimum of 1-year baseline and 6-month outcome period
Evidence of at least 1 prescription for DuoResp Spiromax® during the outcome period excluding the first DuoResp Spiromax® at the index date
Exclusion criteria
For asthma patients: Diagnosis for any chronic respiratory disease diagnosis, except asthma, at any time
Spiromax patients must be registered at practices considered to have a policy of DuoResp® Spiromax® adoption or wholesale change. Such practices will be identified as those at which ≥5 patients change to DuoResp Spiromax® within a three-month period

Table 2: Inclusion and exclusion criteria for phase 2

4.3 Data source

The study will use patient data from the Optimum Patient Care Research Database (OPCRD). The study team work with fully anonymised data, removed of any patient identifiable information. The OPCRD is developed, maintained, and owned by Optimum Patient Care, a social enterprise company that aims to improve patient outcomes through medical research and services. OPC provides evidence-based recommendations to UK general practices through bespoke software and practice reports.

The OPCRD currently comprises longitudinal medical records for over 2.2 million patients from over 550 primary care practices across the UK. The OPCRD contains two types of data: (1) routinely recorded clinical data and (2) questionnaire responses from over 40,000 patients with respiratory conditions. The OPC questionnaires are a compilation of validated questions covering symptoms, disease control, triggers, side effects, quality of life, and unique adherence measures. Indeed the OPCRD is the only database in the UK that complements routinely recorded disease coding and prescribing information with patient-reported outcomes. The OPCRD also links with nationwide practice prescribing data to enable targeted delivery of dataset needs.

The database has received a favourable opinion from the Health Research Authority for clinical research use (REC reference: 15/EM/0150). Governance is provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG)[43] to govern the standard of research conducted on internationally recognised databases. All research using OPCRD will

be registered on established study databases such as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)[44].

4.4 Study outcome analysis

The percentage of patients change to DuoResp Spiromax, who do not receive ≥1 prescription[12] for ICS/LABA during 6 month outcome period will be defined as persisting with their change to DuoResp Spiromax. Some patients will change back to Symbicort/Seretide due to resistance to change rather than persistence of the new therapy. A change-back rate of >17% will be evaluated as potentially indicative of non-acceptibility of the change.[5]

4.5 Statistical analysis

4.5.1 Software used

Statistical analysis will be performed using SPSS Statistics version 23 software (IBM SPSS Statistics, Feltham, Middlesex, United Kingdom) and SAS version 9.3 software (SAS Institute, Marlow, Buckinghamshire, United Kingdom).

4.5.2 Analysis

Number and proportion of patients persisting with the change to DuoResp® Spiromax® from Symbicort® Turbohaler® / Seretide® Accuhaler® will be calculated and reported.

4.6 Power calculation

Based on an expected "change-back" probability of approximately 0.12 (12%) from a previous study[6] among patients changing from one device to another at their prescription date, a sample size of 115 patients would be sufficient to construct a 95% one-sided confidence interval with an upper bound of less than 0.17 (17%) to power the evaluation of DuoResp® Spiromax® "change success".

[12] Not including prescription issued at their date of first prescription and with no Symbicort/Seretide prescriptions during outcome period

5.0 Phase 3

5.1 Study design

Historical cohort database study involving patients who change their FDC therapy to DuoResp® Spiromax® from ICS/LABA FDC (either Symbicort® Turbohaler® or Seretide® Accuhaler®). Patients with a minimum of one year data prior to (baseline) and one year data post (outcome) the date that they receive their first DuoResp® Spiromax® prescription will be included in the study. For the primary outcomes, the patients' baseline data will be compared to their outcome data.

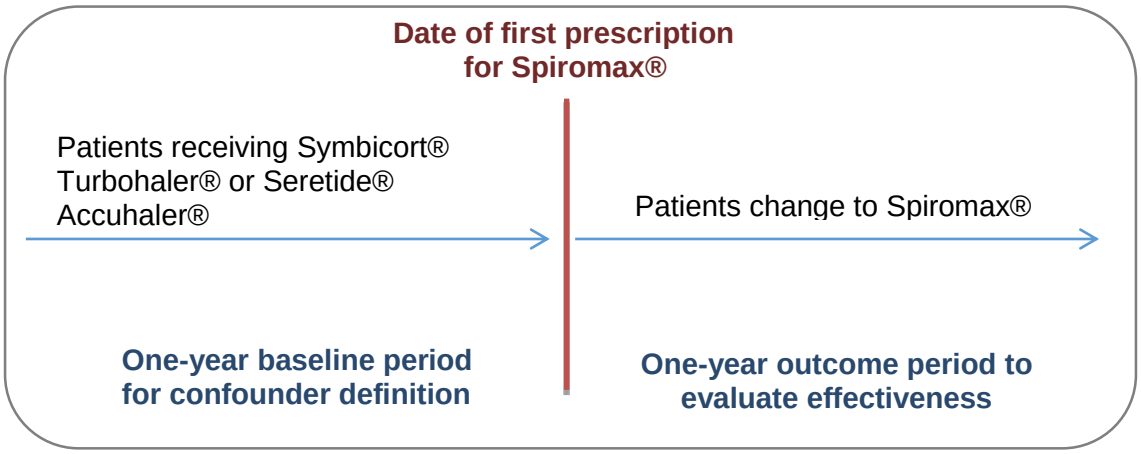

Figure 3: Study design for Phase 3.

5.2 Study population

5.2.1 Inclusion and exclusion criteria

Inclusion criteria
Asthma patients: • Aged ≥18 years at first prescription for DuoResp® Spiromax® • Evidence of asthma, defined as adiagnostic code and/or ≥2 prescriptions for asthma therapy [13] during the baseline year
COPD patients: • Aged ≥40 years at first prescription for DuoResp® Spiromax® • A diagnostic Read code for COPD qualifying for the inclusion in the register of patients with COPD, which GP practices in the UK maintain for the Quality Outcomes Framework. This requires a post-bronchodilator FEV_1/FVC <0.70
Evidence of at least 3 prescriptions for ICS/LABA FDC (Symbicort® Turbohaler® or Seretide® Accuhaler®) therapy during the baseline period

[13] Includes prescriptions for bronchodilators including beta2-agonists, anticholinergics, theophylline or combination therapy, inhaled corticosteroids, combination inhaled corticosteroids and bronchodilator therapy

Evidence of at least 1 prescription for DuoResp® Spiromax® during outcome period excluding the first DuoResp® Spiromax® prescription
Continuous study period comprising of a minimum of 1-year baseline and 1-year outcome period
Exclusion criteria
For asthma patients: Diagnosis for any chronic respiratory disease diagnosis, except asthma, at any time
DuoResp® Spiromax® patients must be registered at practices considered to have a policy of DuoResp® Spiromax® adoption or wholesale change. Such practices will be identified as those at which ≥5 patients change to DuoResp® Spiromax® within a three-month period

Table 4: Inclusion and exclusion criteria for phase 3

5.3 Data source

The study will use patient data from the Optimum Patient Care Research Database (OPCRD). The study team work with fully anonymised data, removed of any patient identifiable information. The OPCRD is developed, maintained, and owned by Optimum Patient Care, a social enterprise company that aims to improve patient outcomes through medical research and services. OPC provides evidence-based recommendations to UK general practices through bespoke software and practice reports.

The OPCRD currently comprises longitudinal medical records for over 2.2 million patients from over 550 primary care practices across the UK. The OPCRD contains two types of data: (1) routinely recorded clinical data and (2) questionnaire responses from over 40,000 patients with respiratory conditions. The OPC questionnaires are a compilation of validated questions covering symptoms, disease control, triggers, side effects, quality of life, and unique adherence measures. Indeed the OPCRD is the only database in the UK that complements routinely recorded disease coding and prescribing information with patient-reported outcomes. The OPCRD also links with nationwide practice prescribing data to enable targeted delivery of dataset needs.

The database has received a favourable opinion from the Health Research Authority for clinical research use (REC reference: 15/EM/0150). Governance is provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG)[43] to govern the standard of research conducted on internationally recognised databases. All research using OPCRD will be registered on established study databases such as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)[44].

5.4 Study variables

5.4.1 Demographics

- Age and gender (at the time of the clinical review)
- BMI, closest to the index date: defined as the ratio of weight (kg) to squared height (m^2), and categorised as 'underweight' (< 18.5 kg/m^2), 'normal weight' (≥ 18.5 kg/m^2 and < 25 kg/m^2), 'overweight' (≥ 25 kg/m^2 and < 30 kg/m^2) and 'obese' (≥ 30 kg/m^2)
- Smoking status, closest to the index date: non-smoker, current smoker and ex-smoker

5.4.2 Comorbdities

Comorbidities and co-medications of interest will include:

- Asthma for COPD cohort (ACOS)*
- Ischaemic heart disease*
- Heart failure*
- Diabetes*
- Pneumonia*
- Gastro-oesophageal reflux disease (GERD)**
- Allergic and non-allergic rhinitis**
- Other chronic lung diseases*
- Charlson comorbidity index score[14] (CCI) score - a weighted index that takes into account the number and seriousness of comorbid diseases to estimate the risk of death from comorbid diseases[52]

5.4.3 Lung function

- Forced Expiratory Flow in one second (FEV_1), closest to the index date: refers to the forced expiratory volume in one second, expressed as a percentage of the predicted normal value
- Peak Expiratory Flow (PEF), closest to IPD: refers to the the maximum flow at the outset of forced expiration

[14]Based on the International Classification of Diseases, 9th revision (ICD-9) predicts the ten-year mortality for patients with comorbidities, where each comorbidity is assigned a score.

* with a diagnostic code recorded at any time prior to or at the last extraction date

** with a diagnostic code recorded + treatment course at any time prior to or at the last extraction date

- FEV_1/ Forced Vital Capacity (FVC) ratio, closest to IPD: represents the proportion of a person's vital capacity that they are able to expire in the first second of forced expiration

5.4.4 Disease severity and control

COPD patients:

- GOLD group, closest to the index date: based on 2014 GOLD guidelines:[9]
  - A = low risk, less symptoms: mMRC of ≤ 1; and FEV_1 ≥ 50% and/or ≤ 1 exacerbation per year (with no hospitalisations for exacerbations)
  - B = low risk, more symptoms: mMRC of ≥ 2; and FEV_1 ≥ 50% and/or ≤ 1 exacerbation per year (with no hospitalisations for exacerbations)
  - C = high risk, less symptoms: mMRC of ≤ 1; and FEV_1 < 50% and/or ≥ 2 exacerbations per year (or ≥ 1 hospitalisation for exacerbation)
  - D = high risk, more symptoms: mMRC of ≥ 2; and FEV_1 < 50% and/or ≥ 2 exacerbations per year (or ≥ 1 hospitalisation for exacerbation)
- Moderate/severe COPD exacerbations, defined as the occurrence of any of the following:[15]
  - Acute course of oral corticosteroids[16]
  - Antibiotics prescribed with a lower respiratory consultation[17]
  - COPD-related, unscheduled hospital admission / emergency department attendance (i.e. severe exacerbation)[18]

[15] Where > 1 oral corticosteroid courses / hospitalisations / antibiotic prescriptions occurred within 2 weeks of each other, they will be considered to be the result of the same exacerbation (and only counted once).

[16] Defined as any of the following: (a) courses that are definitely not maintenance therapy (defined as prescriptions for Prednisolone with daily dosing instructions of ≤ 10 mg, and for 1 mg or 2.5 mg Prednisolone tablets where daily dosing instructions are not available); (b) courses where dosing instructions suggest exacerbation treatment (e.g. 6-1 reducing, or 30 mg as directed); and (c) courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions.

[17] Identified by Read codes for any of the following: (a) lower respiratory diagnosis (including asthma, COPD and lower respiratory tract infection codes); (b) asthma/COPD review codes excluding any monitoring letter codes; (c) lung function and/or asthma monitoring codes; and (d) any additional respiratory examinations, referrals, chest x-rays, or events.

[18] Identified by Read codes for any of the following: (a) definite COPD emergency attendance or definite COPD hospital admission; (b) generic hospitalisation code which has been recorded on the same day as a lower respiratory consultation (see footnote above, refers to (a) - (c) only and excluding those where the lower respiratory code was for a lung function test only).

- mMRC score, closest to the index date: refers to the modified British Medical Research Council questionnaire for assessing the severity of breathlessness, graded from 0, lowest score of breathlessness, to 4, highest score of breathlessness.[9] Both routine medical practice recorded and patient questionnaire mMRC scores will be used, with the most recent score taking precedence
- CAT score, based on COPD Assessment Test (where available)

Asthma patients

- GINA steps of treatment 1-5, closest to the index date (based on GINA guidelines 2014
- GINA control, closest to the index date (based on GINA guidelines 2014)
    - Step 1. Symptoms <once weekly; brief exacerbaitons; nocturnal symptoms ≤twice monthly; PEF or FEV_1 variability <20%
    - Step 2. Symptoms >once weekly but <once daily; exacerbaitons may affect activity and sleep; nocturnal symptoms >twice monthly; PEF or FEV_1 variability 20-30%
    - Step 3. Symptoms daily; exacerbaitons may affect activity and sleep; nocturnal symptoms >once weekly; PEF or FEV_1 variability >30%
    - Step 4. Symptoms daily; frequent exacerbaitons; frequent nocturnal asthma symptoms; limitations of physical activities; PEF or FEV_1 variability >30%
- Severe asthma exacerbation event based on the ATS/ERS Position Statement is defined as an occurrence[19] of asthma related
    - Hospital admissions. Asthma-Related Hospitalisations: consists of either a definite Asthma Emergency Attendance or a definite Asthma Hospital Admission; OR a generic hospitalisation Read code which has been recorded on the same day as a Lower Respiratory Consultationv (see below; (a) – (c) only and excluding where the only lower respiratory code recorded on that day was for a lung function test) OR
    - A&E attendance, OR
    - Acute course of oral corticosteroids 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

[19] Where ≥1 oral corticosteroid course / hospitalisation occurs 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).

all courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions; “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.

- Acute respiratory event is defined as an occurrence of the following:
    e. Asthma-related hospital admission OR
    f. A&E attendance, OR
    g. An acute course of oral steroids; OR
    h. Antibiotics prescribed with lower respiratory consultation

- Risk Domain Asthma Control (RDAC)
  Controlled asthma is defined as the absence of the following aspects of asthma risk during the outcome year:
    c. Asthma-related hospital admission AND A&E attendance, AND out-patient department attendance
    d. Acute course of oral corticosteroids with evidence of a lower respiratory consultation

5.4.5 Prescriptions

- Respiratory-related therapies, in the year prior to the index date:
    - Short-acting β_2 agonist (SABA) and/or short-acting muscarinic antagonist (SAMA)
    - Long-acting β_2 agonist (LABA)
    - Long-acting muscarinic antagonist (LAMA)
    - Inhaled corticosteroids (ICS)
    - Fixed combinations of LABA and ICS
    - LTRA

  SABA reliever usage, in the year prior to the index date: average daily dose in µg/day calculated as

  ([Count of inhalers x doses in pack] / 365) x µg strength

5.5 Study endpoints

5.5.1 Primary endpoint

Non-inferiority of DuoResp® Spiromax® to other LABA/ICS FDCs (either Symbicort® Turbohaler® or Seretide® Accuhaler®) in terms of patients achieving Risk Domain Control defined as follows:

Successful – *absence of:*

- Asthma- or COPD- related:
  - Hospital admission OR A&E attendance OR
  - Unscheduled out-patient department attendance; AND
- Prescriptions for acute courses of oral corticosteroids; OR
- Antibiotics prescribed with lower respiratory consultation

Unsuccessful - *all others*

In the case of non-inferiority being met, a test of superiority will be conducted.

5.5.2 Secondary effectiveness endpoints

Asthma patients

- Change in severe exacerbation rate (based on the ATS/ERS Task Force Position Statement)[7], were asthma-related exacerbations defined as:
  - Hospital attendance/admission: consists of either a definite Asthma Emergency Attendance or a definite Asthma Hospital Admission; OR a generic hospitalisation Read code which has been recorded on the same day as a Lower Respiratory Consultation (see below) excluding where the only lower respiratory code recorded on that day was for a lung function test.
    - Evidence of a Respiratory Consultation: consists of any Lower Respiratory Consultation and/or any additional respiratory examinations, referrals, chest x-rays or events
    - Lower Respiratory Consultations - consist of the following: a) Lower Respiratory read codes (including Asthma and LRTI Read codes); b) Asthma review codes excl. any monitoring letter codes; c) Lung function and/or asthma monitoring AND/OR
  - A & E attendance AND/OR
  - Acute use of oral corticosteroids with evidence of respiratory review
- Change in treatment stability, defined as:
  - Achieved Risk Domain Asthma Control AND
  - No increased dose of AND/OR use of additional therapy defined as long-acting bronchodilator (LABA), theophylline, leukotriene receptor antagonists (LTRAs)

  - No increase in dose, change in delivery device, change in type of ICS AND/OR use of additional therapy as defined by LABAs, theophylline, LTRAs, long-acting muscarinic antagonists (LAMAs)
- Change in SABA usage - average daily SABA dosage during outcome year
- Change in number of lower respiratory hospitalisations, defined as:
  - Definite: Hospitalisations coded with a lower respiratory code, including asthma and LRTI codes; OR a generic hospitalisation Read code that has been recorded on the same day as a Lower Respiratory Consultation
  - Definite + Probable: Hospitalisations occurring within a 7-day window (either side of the hospitalisation date) of a lower respiratory Read code

COPD patients

- Change in COPD exacerbation rate (based on the ATS/ERS Task Force Position Statement)[7], defined as:
  - Unscheduled hospital admission / A&E attendance; OR
  - An acute course of oral corticosteroids; OR
  - Antibiotics prescribed with lower respiratory consultation
- Change in treatment stability, defined as:
  - Achieved treatment success AND
  - No increased dose of AND/OR use of additional therapy defined as long-acting bronchodilator (LABA), theophylline
  - No increase in dose, change in delivery device, change in type of ICS AND/OR use of additional therapy as defined by LABAs, theophylline, long-acting muscarinic antagonists (LAMAs)
- Change in SABA usage - average daily SABA dosage during outcome year
- Change in number of lower respiratory hospitalisations, defined as:
  - Definite: Hospitalisations coded with a lower respiratory code, including COPD and LRTI codes; OR a generic hospitalisation Read code that has been recorded on the same day as a Lower Respiratory Consultation
  - Definite + Probable: Hospitalisations occurring within a 7-day window (either side of the hospitalisation date) of a lower respiratory Read code

5.5.3 Secondary cost-related endpoints

- Change in asthma- or COPD-related costs (per patient per year) for each of the categories below individually and in total, including:
  - Respiratory drug prescriptions, including ICS, SABA, LABA, LAMA, LTRA, theophylline, acute oral corticosteroids and antibiotics for LRTIs;

- Primary care consultations;
- Respiratory-related hospital costs;

5.6 Statistical analysis

5.6.1 Software used

Statistical analysis will be performed using SPSS Statistics version 23 software (IBM SPSS Statistics, Feltham, Middlesex, United Kingdom) and SAS version 9.3 software (SAS Institute, Marlow, Buckinghamshire, United Kingdom).

5.6.2 Primary outcome: test of non-inferiority

Conditional logistic regression of the within-patient difference in the primary outcome from baseline to outcome will be conducted to provide a 95% confidence interval with which to assess non-inferiority. For the primary outcome, non-inferiority will be claimed if the lower bound of the 95% confidence interval is above -10%. In the event that non-inferiority is achieved, superiority will be tested.

5.6.3 Comparative statistics

Outcome vs baseline data of patients with asthma and COPD changing from
ICS/LABA FDC DPI to DuoResp® Spiromax® split by disease diagnosis and outcomes:

- Scale variables (interval or ratio): Wilcoxon signed rank test
- Categorical variables: Marginal homogeneity test or McNemar's test (dichotomous variables)
- Statistically significant results are defined as $p<0.05$

Results will be reported as:

- Variables measured on the interval/ratio scale:
  - Sample size (n) and percentage non-missing
  - Median and inter-quartile range (25th and 75th percentiles)
- Categorical variables:
  - Sample size (n)
  - Count and percentage by category (distribution)

5.6.4 Secondary outcome.

The secondary endpoints analysis will include:

- Exacerbation & hospitalisation rates analyses using conditional poisson regression.
- Treatment Stability analysis using conditional logistic regression.
- SABA usage analysis using conditional ordinal logistic regression.

5.7 Power calculation

When the sample size is **393**, a paired test with a 0.050 one-sided significance level will have 90% power to reject the null hypothesis that the proportions are not equivalent (the difference in proportions, DuoResp® Spiromax® - Control, is 0.10 or further from zero in the same direction) when the expected difference in proportions is 0.000, assuming that the proportion of discordant pairs is 0.458. This assumption is based on previous studies showing that a weighted average of 71.6% of asthma and COPD patients prescribed FDC therapy have no exacerbations over a one year period.[8,9]

6.0 Phase 4

6.1 Study design

Phase 4 is a matched, historic cohort study, consisting of a one year baseline period and a one year outcome period. Two patient cohorts will be analysed:

1) COPD and/or asthma patients who were on either Symbicort® Turbohaler® or Seretide® Accuhaler® during their baseline period and changed to DuoResp® Spiromax®
2) COPD and/or asthma patients who were on either Symbicort® Turbohaler® or Seretide® Accuhaler® during their baseline period and received a continued prescription for same ICS/LABA FDC in outcome period

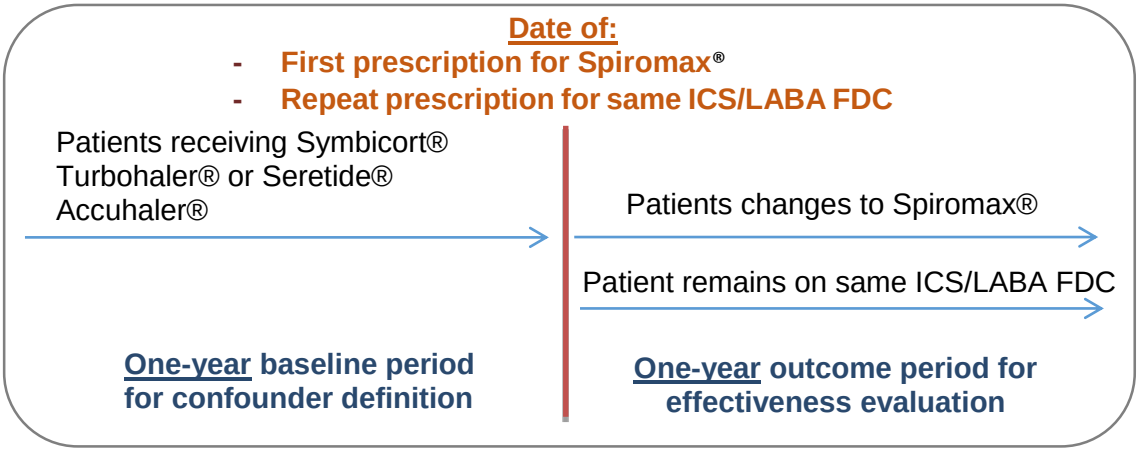

Figure 4: Study design for phase 4

6.2 Study population

6.2.1 Inclusion and exclusion criteria

Inclusion criteria
Asthma patients: • Aged ≥18 years at first prescription for Spiromax® • Evidence of asthma, defined as adiagnostic code and/or ≥2 prescriptions for asthma therapy [20] during the baseline year
COPD patients: • Aged ≥40 years at first prescription for Spiromax® • A diagnostic Read code for COPD qualifying for the inclusion in the register of patients with COPD, which GP practices in the UK maintain for the Quality Outcomes Framework. This requires a post-bronchodilator FEV_1/FVC <0.70

[20] Includes prescriptions for bronchodilators including beta2-agonists, anticholinergics, theophylline or combination therapy, inhaled corticosteroids, combination inhaled corticosteroids and bronchodilator therapy

Evidence of at least 3 prescriptions for either Symbicort® Turbohaler® or Seretide® Accuhaler® ICS/LABA FDC therapy during the baseline period
• Spiromax® initiation cohort: evidence of at least 1 prescription for Spiromax® during the outcome period excluding the first Spiromax® prescription • ICS/LBA FDC continuation cohort: evidence of at least 1 prescription for ICS/LABA FDC during outcome period (same therapy as that prescribed in baseline)
Continuous study period comprising of a minimum of 1-year baseline and 1-year outcome period
Exclusion criteria
For asthma patients: Diagnosis for any chronic respiratory disease diagnosis, except asthma, at any time
Spiromax® patients must be registered at practices considered to have a policy of Spiromax® adoption or wholesale change. Such practices will be identified as those at which ≥5 patients change to Spiromax® within a three-month period

Table 5. Inclusion/exclusion criteria for phase 4

6.3 Data source

The study will use patient data from the Optimum Patient Care Research Database (OPCRD). The study team work with fully anonymised data, removed of any patient identifiable information. The OPCRD is developed, maintained, and owned by Optimum Patient Care, a social enterprise company that aims to improve patient outcomes through medical research and services. OPC provides evidence-based recommendations to UK general practices through bespoke software and practice reports.

The OPCRD currently comprises longitudinal medical records for over 2.2 million patients from over 550 primary care practices across the UK. The OPCRD contains two types of data: (1) routinely recorded clinical data and (2) questionnaire responses from over 40,000 patients with respiratory conditions. The OPC questionnaires are a compilation of validated questions covering symptoms, disease control, triggers, side effects, quality of life, and unique adherence measures. Indeed the OPCRD is the only database in the UK that complements routinely recorded disease coding and prescribing information with patient-reported outcomes. The OPCRD also links with nationwide practice prescribing data to enable targeted delivery of dataset needs.

The database has received a favourable opinion from the Health Research Authority for clinical research use (REC reference: 15/EM/0150). Governance is provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG)[43] to govern the standard of research conducted on internationally recognised databases. All research using OPCRD will

be registered on established study databases such as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)[44].

6.4 Study variables

6.4.1 Demographics

- Age and gender (at the time of the clinical review)
- BMI, closest to the index date: defined as the ratio of weight (kg) to squared height (m^2), and categorised as 'underweight' (< 18.5 kg/m^2), 'normal weight' (≥ 18.5 kg/m^2 and < 25 kg/m^2), 'overweight' (≥ 25 kg/m^2 and < 30 kg/m^2) and 'obese' (≥ 30 kg/m^2)
- Smoking status, closest to the index date: non-smoker, current smoker and ex-smoker

6.4.2 Comorbidities

Comorbidities and co-medications of interest will include:

- Asthma for COPD cohort (ACOS)*
- Ischaemic heart disease*
- Heart failure*
- Diabetes*
- Pneumonia*
- Gastro-oesophageal reflux disease (GERD)**
- Allergic and non-allergic rhinitis**
- Other chronic lung diseases*
- Charlson comorbidity index score[21] (CCI) score - a weighted index that takes into account the number and seriousness of comorbid diseases to estimate the risk of death from comorbid diseases[52]

[21]Based on the International Classification of Diseases, 9th revision (ICD-9) predicts the ten-year mortality for patients with comorbidities, where each comorbidity is assigned a score.

* with a diagnostic code recorded at any time prior to or at the last extraction date

** with a diagnostic code recorded + treatment course at any time prior to or at the last extraction date

6.4.3 Lung function

- Forced Expiratory Flow in one second (FEV_1), closest to the index date: refers to the forced expiratory volume in one second, expressed as a percentage of the predicted normal value
- Peak Expiratory Flow (PEF), closest to IPD: refers to the the maximum flow at the outset of forced expiration
- FEV_1/ Forced Vital Capacity (FVC) ratio, closest to IPD: represents the proportion of a person's vital capacity that they are able to expire in the first second of forced expiration

6.4.4 Disease severity and control

COPD patients:

- GOLD group, closest to the index date: based on 2014 GOLD guidelines:[9]
  - A = low risk, less symptoms: mMRC of ≤ 1; and FEV_1 ≥ 50% and/or ≤ 1 exacerbation per year (with no hospitalisations for exacerbations)
  - B = low risk, more symptoms: mMRC of ≥ 2; and FEV_1 ≥ 50% and/or ≤ 1 exacerbation per year (with no hospitalisations for exacerbations)
  - C = high risk, less symptoms: mMRC of ≤ 1; and FEV_1 < 50% and/or ≥ 2 exacerbations per year (or ≥ 1 hospitalisation for exacerbation)
  - D = high risk, more symptoms: mMRC of ≥ 2; and FEV_1 < 50% and/or ≥ 2 exacerbations per year (or ≥ 1 hospitalisation for exacerbation)
- Moderate/severe COPD exacerbations, defined as the occurrence of any of the following:[22]
  - Acute course of oral corticosteroids[23]

[22] Where > 1 oral corticosteroid courses / hospitalisations / antibiotic prescriptions occurred within 2 weeks of each other, they will be considered to be the result of the same exacerbation (and only counted once).

[23] Defined as any of the following: (a) courses that are definitely not maintenance therapy (defined as prescriptions for Prednisolone with daily dosing instructions of ≤ 10 mg, and for 1 mg or 2.5 mg Prednisolone tablets where daily dosing instructions are not available); (b) courses where dosing instructions suggest exacerbation treatment (e.g. 6-1 reducing, or 30 mg as directed); and (c) courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions.

- Antibiotics prescribed with a lower respiratory consultation[24]
- COPD-related, unscheduled hospital admission / emergency department attendance (i.e. severe exacerbation)[25]

- mMRC score, closest to the index date: refers to the modified British Medical Research Council questionnaire for assessing the severity of breathlessness, graded from 0, lowest score of breathlessness, to 4, highest score of breathlessness.[9] Both routine medical practice recorded and patient questionnaire mMRC scores will be used, with the most recent score taking precedence
- CAT score, based on COPD Assessment Test (where available)

Asthma patients

- GINA steps of treatment 1-5, closest to the index date (based on GINA guidelines 2014
- GINA control, closest to the index date (based on GINA guidelines 2014)
  - Step 1. Symptoms <once weekly; brief exacerbaitons; nocturnal symptoms ≤twice monthly; PEF or FEV_1 variability <20%
  - Step 2. Symptoms >once weekly but <once daily; exacerbaitons may affect activity and sleep; nocturnal symptoms >twice monthly; PEF or FEV_1 variability 20-30%
  - Step 3. Symptoms daily; exacerbaitons may affect activity and sleep; nocturnal symptoms >once weekly; PEF or FEV_1 variability >30%
  - Step 4. Symptoms daily; frequent exacerbaitons; frequent nocturnal asthma symptoms; limitations of physical activities; PEF or FEV_1 variability >30%
- Severe asthma exacerbation event based on the ATS/ERS Position Statement is defined as an occurrence[26] of asthma related
  - Hospital admissions. Asthma-Related Hospitalisations: consists of either a definite Asthma Emergency Attendance or a definite Asthma Hospital Admission;

[24] Identified by Read codes for any of the following: (a) lower respiratory diagnosis (including asthma, COPD and lower respiratory tract infection codes); (b) asthma/COPD review codes excluding any monitoring letter codes; (c) lung function and/or asthma monitoring codes; and (d) any additional respiratory examinations, referrals, chest x-rays, or events.

[25] Identified by Read codes for any of the following: (a) definite COPD emergency attendance or definite COPD hospital admission; (b) generic hospitalisation code which has been recorded on the same day as a lower respiratory consultation (see footnote above, refers to (a) - (c) only and excluding those where the lower respiratory code was for a lung function test only).

[26] Where ≥1 oral corticosteroid course / hospitalisation occurs 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).

OR a generic hospitalisation Read code which has been recorded on the same day as a Lower Respiratory Consultationv (see below; (a) – (c) only and excluding where the only lower respiratory code recorded on that day was for a lung function test) OR

- A&E attendance, OR
- Acute course of oral corticosteroids 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; "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.

- Acute respiratory event is defined as an occurrence of the following:
    a. Asthma-related hospital admission OR
    b. A&E attendance, OR
    c. An acute course of oral steroids; OR
    d. Antibiotics prescribed with lower respiratory consultation

- Risk Domain Asthma Control (RDAC)
  Controlled asthma is defined as the absence of the following aspects of asthma risk during the outcome year:
    a. Asthma-related hospital admission AND A&E attendance, AND out-patient department attendance
    b. Acute course of oral corticosteroids with evidence of a lower respiratory consultation

6.4.5 Prescriptions

- Respiratory-related therapies, in the year prior to the index date:
    - Short-acting β_2 agonist (SABA) and/or short-acting muscarinic antagonist (SAMA)
    - Long-acting β_2 agonist (LABA)
    - Long-acting muscarinic antagonist (LAMA)
    - Inhaled corticosteroids (ICS)

- Fixed combinations of LABA and ICS
- LTRA

SABA reliever usage, in the year prior to the index date: average daily dose in µg/day calculated as

([Count of inhalers x doses in pack] / 365) x µg strength

6.5 Study endpoints

6.5.1 Primary endpoint

Non-inferiority of DuoResp® Spiromax® to other ICS/LABA FDC (either Symbicort® Turbohaler® or Seretide® Accuhaler®) DPIs
in terms of patients achieving Risk Domain Control defined as follows:

Successful – *absence of:*

- Asthma- or COPD- related:
  - Hospital admission OR A&E attendance OR
  - Unscheduled out-patient department attendance; AND
- Prescriptions for acute courses of oral corticosteroids; OR
- Antibiotics prescribed with lower respiratory consultation

Unsuccessful - *all others*

In the case of non-inferiority being met, a test of superiority will be conducted.

6.5.2 Secondary effectiveness endpoints

Asthma patients

- Change in severe exacerbation rate (based on the ATS/ERS Task Force Position Statement)[7], were asthma-related exacerbations defined as:
  - Hospital attendance/admission: consists of either a definite Asthma Emergency Attendance or a definite Asthma Hospital Admission; OR a generic hospitalisation Read code which has been recorded on the same day as a Lower Respiratory Consultation (see below) excluding where the only lower respiratory code recorded on that day was for a lung function test.
    - Evidence of a Respiratory Consultation: consists of any Lower Respiratory Consultation and/or any additional respiratory examinations, referrals, chest x-rays or events

- Lower Respiratory Consultations - consist of the following: a) Lower Respiratory read codes (including Asthma and LRTI Read codes); b) Asthma review codes excl. any monitoring letter codes; c) Lung function and/or asthma monitoring AND/OR
  - A & E attendance AND/OR
  - Acute use of oral corticosteroids with evidence of respiratory review

- Change in treatment stability, defined as:
  - Achieved Risk Domain Asthma Control AND
  - No increased dose of AND/OR use of additional therapy defined as long-acting bronchodilator (LABA), theophylline, leukotriene receptor antagonists (LTRAs)
  - No increase in dose, change in delivery device, change in type of ICS AND/OR use of additional therapy as defined by LABAs, theophylline, LTRAs, long-acting muscarinic antagonists (LAMAs)

- Change in SABA usage - average daily SABA dosage during outcome year

- Change in number of lower respiratory hospitalisations, defined as:
  - Definite: Hospitalisations coded with a lower respiratory code, including asthma and LRTI codes; OR a generic hospitalisation Read code that has been recorded on the same day as a Lower Respiratory Consultation
  - Definite + Probable: Hospitalisations occurring within a 7-day window (either side of the hospitalisation date) of a lower respiratory Read code

COPD patients

- Change in COPD exacerbation rate (based on the ATS/ERS Task Force Position Statement)[7], defined as:
  - Unscheduled hospital admission / A&E attendance; OR
  - An acute course of oral corticosteroids; OR
  - Antibiotics prescribed with lower respiratory consultation

- Change in treatment stability, defined as:
  - Achieved treatment success AND
  - No increased dose of AND/OR use of additional therapy defined as long-acting bronchodilator (LABA), theophylline

  - No increase in dose, change in delivery device, change in type of ICS AND/OR use of additional therapy as defined by LABAs, theophylline, long-acting muscarinic antagonists (LAMAs)

- Change in SABA usage - average daily SABA dosage during outcome year

- Change in number of lower respiratory hospitalisations, defined as:
  - Definite: Hospitalisations coded with a lower respiratory code, including COPD and LRTI codes; OR a generic hospitalisation Read code that has been recorded on the same day as a Lower Respiratory Consultation
  - Definite + Probable: Hospitalisations occurring within a 7-day window (either side of the hospitalisation date) of a lower respiratory Read code

6.5.3 Secondary cost-effectiveness endpoints

Change in asthma-related or COPD-related total and disaggregated costs (per patient per year) in patients switched to DuoResp® Spiromax® from Symbicort® Turbohaler® or Seretide® Accuhaler® or continued treatment on other ICS/LABA FDC DPIs, including:

  - Respiratory drug prescriptions, including ICS, SABA, LABA, LAMA, LTRA, theophylline, acute oral corticosteroids and antibiotics for LRTIs;
  - Primary care consultations;
  - Respiratory-related hospital costs
- Cost effectiveness will be analysed using incremental costs effectiveness ratio (ICER[27]) with differencing costs in the numerator and differencing effectiveness in the denominator between study groups.

6.6 Statistical analysis

[27] ICER defined as difference in medication costs and primary- and secondary-care costs in the numerator and difference in exacerbations in the denominator to estimate cost-effectiveness between study groups. Exacerbations include: hospital admissions, emergency room visits, unscheduled outpatient visits, and oral steroid prescriptions measured between groups and between baseline and 6 month and 12 month follow-up time periods.

6.6.1 Software used

Statistical analysis will be performed using SPSS Statistics version 21 software (IBM SPSS Statistics, Feltham, Middlesex, United Kingdom) and SAS version 9.3 software (SAS Institute, Marlow, Buckinghamshire, United Kingdom).

6.6.2 Summary statistical analyses

Prior to statistical analysis of the outcomes, an exploratory analysis of baseline variables for each cohort will be carried out for data validation and to investigate possible baseline differences between the two cohorts in order to establish whether or not the analysis may benefit from matching.

Treatment groups will be compared referring to endpoints using the following tests:

- Variables measured on the interval/ratio scale:
  - t-test (normal distribution)
  - Mann-Whitney U test (skewed data)
- Categorical variables:
  - Chi-square test

Statistical significance will be set at $p<0.05$.

Baseline differences between cohorts will be evaluated prior to matching (see below) using t-tests, Mann-Whitney U tests or Pearson's Chi-squared tests.

Results will be reported as:

- Variables measured on the interval/ratio scale:
  - Sample size (n) and percentage non-missing
  - Median and inter-quartile range (25th and 75th percentiles)
- Categorical variables:
  - Sample size (n)
  - Count and percentage by category (distribution)

6.6.3 Matching

Patients will be matched on demographics and key measures of disease severity to minimise confounding. Matching variables and categories will be selected based on evaluation of baseline differences between the two cohorts (Mann Whitney/Chi-square test, $p<0.05$) and clinical review of the data. Only unique patients will be selected from the cohorts by random selection process through SAS statistical software to avoid selection bias. Matching will be done separately for asthma and COPD patients.

6.6.4 Summarising baseline outcomes for matched data

Matched patients will be compared in baseline/outcome period by conditional logistic regression by all variables. Summaries will be performed separately for COPD and Asthma patients.

6.6.5 Primary outcome: test of non-inferiority

Conditional logistic regression of the primary outcome between treatment groups will be conducted to provide a 95% confidence interval with which to assess non-inferiority and will be adjusted for baseline confounders. For the primary outcome, non-inferiority will be claimed if the lower bound of the 95% confidence interval is above -10%. In the event that non-inferiority is achieved, superiority will be tested.

The primary analysis will be performed separately for COPD and Asthma patients.

6.6.7 Secondary outcome

The secondary endpoints analysis will include:

- Exacerbation & hospitalisation rates analyses using conditional poisson regression.
- Treatment Stability analysis using conditional logistic regression.
- SABA usage analysis using conditional ordinal logistic regression.

The secondary analyses will be performed separately for COPD and Asthma patients

6.7 Power calculation

When the sample size in each group is 349, a two-group large-sample normal approximation test of proportions with a one-sided 0.050 significance level will have 90% power to reject the null hypothesis that the test and the standard are not equivalent (the difference in proportions, DuoResp® Spiromax® - Control, is 0.10 or further from zero in the same direction) in favour of the alternative hypothesis that the proportions in the two groups are equivalent, assuming that the expected difference in proportions is 0.000 and the proportion in the standard group is 0.716. This assumption is based on previous studies showing that a weighted average of 71.6% of asthma and COPD patients prescribed FDC therapy have no exacerbations over a one year period.[8, 9]

6.8 Confounding factors

Baseline differences will be presented as p-values. As a conservative approach, differences between treatment groups will be considered possibly important if $p < 0.10$. Variables meeting this criterion will be examined for co-linearity and clinical importance to select those used as potential confounders in the regression modelling of outcomes.

6.8.1 Correlations

Pearson and Spearman correlation coefficients (as appropriate) will be calculated between all baseline variables to determine strengths of linear relationships between variables. The correlation coefficients will be considered - in conjunction with clinical interpretation - to identify pairings of variables that may present collinearity issues at the modelling stage. Scatter plots and error bar plots may be used to further investigate relationships (in particular, non-linear relationships).

6.8.2 Predictors of Outcomes

Multivariable analyses will be carried out using the full dataset and each data split to identify baseline variables that are predictive ($p < 0.05$) of outcomes. These will be considered as potential confounders when modelling the outcome variables.

7.0 Regulatory and ethical compliance

The study protocol and design were developed, shall be implemented and reported in accordance with the criteria of the European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and follows the ENCePP Code of Conduct (EMA 2014). Once a final version of the protocol is reviewed and agreed by the advisory group, formal ethics and research management approval of this study will be obtained from the ADEPT Committee, which verifies the scientific and ethical soundness of all research using OPC data. Then, final version of this protocol will be registered with www.encepp.eu

8.0 Data dissemination

Initial results will be presented to the Steering Committee of this study. At least one manuscript containing more detailed results and methodology will be submitted for publications to a journal specialising in respiratory medicine as soon as the analyses are completed and the results are verified.

9.0 Advisory group

Communication with the SC will be held at key milestones: protocol approval, data reviews and validation for phase 1-4, publication planning. Following experts will be included to the steering committee of this study:

- Job van Boven (Netherlands)
- Nicolas Roche (France)
- Leif Bjermer (Sweden)
- Marc Miravitlles (Spain)

10.0 Research team

Research Organisation:

Research in Real-Life (RiRL) Ltd

Chief Investigator:

David Price, Professor of Primary Care Respiratory Medicine and RiRL Director

Mobile: +44 7787905057

Office number: +44 2081233923

Skype ID: respiratoryresearch

Email: david@rirl.org

Other RiRL team members:

General Manager: Humeyra Erdogan (humeyra@rirl.org)

Commercial and Compliance Director: Catherine Hutton (catherine@rirl.org)

Project research lead: Bakhtiyor Khalikulov (bakhtiyor@rirl.org)

Senior statistician: Vicky Thomas (vicky@crs-ltd.org)

Project lead statistician: TBC

Senior data analyst: Derek Skinner (derek@optimumpatientcare.org)

Study sponsor:

Teva

Primary contact

Hicham Benhaddi (Teva)

11.0 Timelines

Phase 1.

Action	Timeline
Study site identification	August – Sept 2015
Data extraction	Sept – Oct 2015
Data Analysis	Oct - Nov 2015
Report delivery/data dissemination	Oct - Nov 2015
Data re-extraction for re-analysis	May 2016

Phase 2.

Action	Timeline
Additional study site identification	Sep – Oct 2015
Data extraction	Oct – Nov 2015
Statistical analysis	Nov - Dec 2015
Report delivery/data dissemination	Dec - Jan 2016

Phase 3.

Action	Timeline
Additional study site identification	Nov 2015 - Jan 2016
Data extraction	April 2016
Statistical analysis	May - June 2016
Report delivery/data dissemination	July - Sep 2016

Phase 4.

Action	Timeline
Additional study site identification	May - July 2016
Data extraction	July - Sept 2016**
Statistical analysis	Oct - Dec 2016
Report delivery/data dissemination	Jan - Apr 2017

* Timeline is a subject to review based on therapy uptake in the market.

** Or earlier if comparator arm of study is easily extracted.

12.0 References

1. Bahadori, Katayoun, Mary M. Doyle-Waters, Carlo Marra, Larry Lynd, Kadria Alasaly, John Swiston, and J. Mark FitzGerald. "Economic burden of asthma: a systematic review." BMC pulmonary medicine 9, no. 1 (2009): 24.
2. World Health Organisation. Chronic respiratory diseases. 2015.
3. World Health Organisation. Chronic respiratory diseases. Asthma. 2015.
4. Global Initiative for Asthma. “Global burden of Asthma”. 2003.
5. World Health Organisation. Chronic respiratory diseases. Burden of COPD. 2015.
6. Lopez, A. D., K. Shibuya, C. Rao, C. D. Mathers, A. L. Hansell, L. S. Held, V. Schmid, and S. Buist. "Chronic obstructive pulmonary disease: current burden and future projections." European Respiratory Journal 27, no. 2 (2006): 397-412.
7. Department of Health, UK. “An outcome strategy for chronic obstructive pulmonary disease (COPD) and Asthma”. 2011.
8. Shahab, L., M. J. Jarvis, J. Britton, and R. West. "Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample." Thorax 61, no. 12 (2006): 1043-1047.
9. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2014.
10. Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L et al. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. Health Technol Assess 2001; 5: 1–149.
11. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, Smaldone GC, Guyatt G, American College of Chest Physicians; American College of Asthma, Allergy, and Immunology: Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest 2005, 127:335-371.
12. Virchow JC, Crompton GK, Dal Negro R, Pedersen S, Magnan A, Seidenberg J, Barnes PJ: Importance of inhaler devices in the management of airway disease. Respiratory Medicine 2008, 102:10-19.
13. Al-Showair RA, Tarsin WY, Assi KH, Pearson SB, Chrystyn H. Can all patients with COPD use the correct inhalation flow with all inhalers and does training help? Respir Med. 2007;101:2395–401. doi: 10.1016/j.rmed.2007.06.008.
14. Giraud, V. and Roche, N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. Eur Respir J. 2002; 19: 246–251
15. Plaza, V. and Sanchis, J. Medical personnel and patient skill in the use of metered dose inhalers: a multicentric study. CESEA Group. Respiration. 1998; 65: 195–198.

16. Hardwell A, Barber V, Hargadon T, McKnight E, Holmes J, Levy ML. Technique training does not improve the ability of most patients to use pressurised metered-dose inhalers (pMDIs) Prim Care Respir J. 2011;20:92–6. doi:10.4104/pcrj.2010. 00088
17. Crompton, G.K. Problems patients have using pressurized aerosol inhalers. Eur J Respir Dis. 1982; 63: 101–104.
18. Crompton, G. and Duncan, J. Clinical assessment of a new breath-activated inhaler. Practitioner. 1989; 233: 268–269.
19. Lenny, J., Innes, J., and Crompton, G. Inappropriate inhaler use: assessment of use and patient preference of seven inhalation devices. Respir Med. 2000; 94: 496–500.
20. Sprossmann, A., Kutschka, F., Enk, M., and Bergmann, K. Factors affecting correct use of metered dose aerosols. Z Erkr Atmungsorgane. 1991; 177: 93–95
21. Crompton, G.K., Dewar, M.H., Allbut, H.M., and Innes, J.A. Inhaler preference and technique in inhaler native subjects; a comparison of HFA and conventional devices. Thorax. 2000; 55: A61
22. Newman, S. et al. Improvement of drug delivery with a breath-activated aerosol for patients with poor inhaler technique. Thorax. 1991; 46: 712–716.
23. Virchow JC. Guidelines versus clinical practice – which therapy and which device. Respir Med. 2004;98(suppl B):S28–34. doi: 10.1016/j.rmed.2004.07.012.
24. Lavorini F, Magnan A, Dubus JC, Voshaar T, Corbetta L, Broeders M, Dekhuijzen R, Sanchis J, Viejo JL, Barnes P, Corrigan C, Levy M, Crompton GK. Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD. Respir Med. 2008 Apr;102(4):593-604. Epub 2007 Dec 20. Review.
25. Molimard M, Raherison C, Lignot S, Depont F, Abouelfath A, Moore N. Assessment of handling of inhaler devices in real life: an observational study in 3811 patients in primary care. J Aerosol Med 2003; 16: 249–254.
26. Newman SP. Dry powder inhalers for optimal drug delivery. Expert Opin Biol Ther 2004; 4: 23–33.
27. Chrystyn H. Is inhalation rate important for a dry powder inhaler? Using the In-Check Dial to identify these rates. Respir Med. 2003;97:181–7. doi: 10.1053/rmed.2003.1351
28. Kamin, W., Genz, T., Roeder, S., Scheuch, G., Cloes, R., Juenemann, R. et al. The inhalation manager: a new computer-based device to assess inhalation technique and drug delivery to the patient. J Aerosol Med. 2003; 16: 21–29
29. European Medicines Agency. EPAR summary for the public. DuoResp Spiromax budesonide / formoterol approval notification: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002348/WC500167184.pdf

30. Williams AE, Chrystyn H: Survey of pharmacists' attitudes towards interchangeable use of dry powder inhalers. Pharm World Sci 2007, 29:221-227.
31. Booker R: Do patients think that dry powder inhalers can be used interchangeably? Int J Clin Pract Suppl 2005, 30-32.
32. Teva Parmaceutical Industries Ltd. Teva Receives European Marketing Authorization for DuoResp Spiromax® for the Treatment of Asthma and COPD. Published April 29, 2014. Available at: http://ir.tevapharm.com/phoenix.zhtml?c=73925&p=irol-newsArticle&ID=1923312
33. NHS New Drugs Online. New Drugs Online Report for budesonide + formoterol. Accessed February 18, 2015. Available at: http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=6246
34. Optimum Patient Care Research Database (OPCRD). Accessed February 2015. Available at: http://www.optimumpatientcare.org/Html_Docs/OPCRD.html
35. Price D, Small I, Haughney J, *et al*. Clinical and cost effectiveness of switching asthma patients from fluticasone-salmeterol to extra-fine particle beclometasone-formoterol: a retrospective matched observational study of real-world patients. Prim Care Respir J 2013;22(4): 439-448
36. Lim et al., Real World Effectiveness of Changing Fixed Dose Combination therapy from Seretide® MDI To Flutiform® in UK asthma Patients. Oral presentation at the IPCRG congress, 2014
37. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014: 43(2):343-73
38. Hagedorn C, Kässner F, Banik N, et al. Influence of salmeterol/fluticasone via single versus separate inhalers on exacerbations in severe/very severe COPD. Respiratory Medicine. 2013:107: 542-549
39. Israel E, Roche N, Martin RJ, et al. Increased Dose of Inhaled Corticosteroid vs. Add-On Long-Acting Beta-Agonist for Step-Up Therapy in Asthma. Manuscript in preparation for submission to Annals ATS. Poster presentation: Real-life effectiveness and cost-effectiveness of asthma step-up options: a UK comparison of extra-fine hydrofluoroalkane-beclometasone and combination therapy. EAC conference, May 30-31, 2014.
40. SAS Institute Inc. 2010. Statistical Analysis with SAS/STAT Software. Available online at: www.SAS.com/offices/europe/uk/technologies/analytics/statistics/stat/ondex.html.
41. IBM SPSS Statistics. 2010. Available online at: www.spss.com/uk/software/statistics/.
42. electronic Medicines Compendium. Available online at: https://www.medicines.org.uk/emc/medicine/29187; https://www.medicines.org.uk/emc/medicine/29186

43. Respiratory Effectiveness Group (REG). Available online at: http://www.effectivenessevaluation.org/
44. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Available online at: http://www.encepp.eu/
45. Barrons R, Pegram A., Borries A. Inhaler device selection: special considerations in elderly patients with chronic obstructive pulmonary disease. Am. J. Health Syst. Pharm., 68 (2011), pp. 1221–1232
46. S.C. Lareau, B.P. Yawn. Improving adherence with inhaler therapy in COPD. Int. J. Chron. Obstruct. Pulmon. Dis., 5 (2010), pp. 401–406.
47. C.S. Rand. Patient adherence with COPD therapy. Eur. Respir. Rev., 14 (2005), pp. 97–101.
48. Teva Pharma BV, 2014. DuoResp Spiromax Summary of Product Characteristics. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002348/human_med_001749
49. Weisfeld, L., Gopalan, G., Shu, Y., Baconnet, B., Shah, T., 2013. Pharmacokinetics (PK) and safety of budesonide plus formoterol (BF) (160/4.5mcg) Spiromax® and BF (200/6mcg) Turbuhaler® following two inhalations (+/–charcoal [char] block) in healthy volunteers (HV). Eur. Respir. J. 42 (Suppl. 57), Abstract #712.
50. Weisfeld, L., Gopalan, G., Shu, Y., Baconnet, B., Shah, T., 2013. Pharmacokinetics (PK) and safety of budesonide plus formoterol (BF) (320/9mcg) Spiromax® and BF (400/12mcg) Turbuhaler®following two inhalations (+/–charcoal [char] block) in healthy volunteers (HV). Eur. Respir. J. 42 (Suppl. 57), Abstract #4630.
51. Arp, J., Goller, M., Keegstra, H., 2013. Uniformity of delivered dose from the first to last dose of the BF Spiromax inhaler in the laboratory and under 'real-world' conditions. Abstract #66 presented at Drug delivery to the lung.
52. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-383.
53. SIGN/BTS. British guideline on the management of asthma. Available online at: http://www.sign.ac.uk/pdf/sign101_asthma_workshops_report.pdf

13.0 APPENDIX

Appendix 1: Summary of inclusion / exclusion criteria for phases 1-4.

Inclusion criteria		Phase 1	Phase 2	Phase 3	Phase 4
Asthma patients	Aged ≥18 years at first prescription for Spiromax	✓	✓	✓	✓
	Evidence of active asthma (a diagnostic code and/or ≥2 prescriptions for asthma therapy[28] during the baseline year)	✓	✓	✓	✓
COPD patients	Aged ≥40 years at first prescription for Spiromax		✓	✓	✓
	Evidence of COPD (COPD diagnosis based on RIRL COPD diagnostic codes[29] and ≥2 prescriptions for COPD therapy**Error! Bookmark not defined.** during baseline year)		✓	✓	✓
Evidence of at least 1 prescription for FDC therapy during the baseline period		✓	✓	✓	✓
One year of continuous practice data prior to their first prescription for Spiromax		✓	✓	✓	✓
Evidence of at least 1 prescription for Symbicort or Seretide therapy during the baseline period			✓	✓	✓
Continuous study period comprising of a minimum of 1-year baseline and 6-month outcome period			✓	✓	✓
Evidence of at least 2 prescriptions for Symbicort or Seretide therapy during the baseline period			✓	✓	✓
Evidence of at least 1 prescription for Spiromax® during outcome period excluding the first Spiromax® prescription			✓	✓	✓
Continuous study period comprising of a minimum of 1-year baseline and 1-year outcome period			✓	✓	✓
Evidence of at least 1 prescription for Seretide® / Symbicort® during outcome period (same therapy as that prescribed in baseline)			✓	✓	✓
Exclusion criteria					
Prescribed Spiromax® outside of the licensing conditions		✓			

[28] Includes prescriptions for bronchodilators including beta2-agonists, anticholinergics, theophylline or combination therapy, inhaled corticosteroids, combination inhaled corticosteroids and bronchodilator therapy

[29] Included COPD diagnosis Read codes based on QOF diagnostic Read codes and screening codes

Appendix 2: Definitions: variables and categories.

- Age and gender (at the time of the clinical review)
- BMI, closest to the index date: defined as the ratio of weight (kg) to squared height (m^2), and categorised as 'underweight' (< 18.5 kg/m^2), 'normal weight' (≥ 18.5 kg/m^2 and < 25 kg/m^2), 'overweight' (≥ 25 kg/m^2 and < 30 kg/m^2) and 'obese' (≥ 30 kg/m^2)
- Smoking status, closest to the index date: non-smoker, current smoker and ex-smoker
- GOLD group, closest to the index date: based on 2014 GOLD guidelines:[7]
    - A = low risk, less symptoms: mMRC of ≤ 1; and FEV_1 ≥ 50% and/or ≤ 1 exacerbation per year (with no hospitalisations for exacerbations)
    - B = low risk, more symptoms: mMRC of ≥ 2; and FEV_1 ≥ 50% and/or ≤ 1 exacerbation per year (with no hospitalisations for exacerbations)
    - C = high risk, less symptoms: mMRC of ≤ 1; and FEV_1 < 50% and/or ≥ 2 exacerbations per year (or ≥ 1 hospitalisation for exacerbation)
    - D = high risk, more symptoms: mMRC of ≥ 2; and FEV_1 < 50% and/or ≥ 2 exacerbations per year (or ≥ 1 hospitalisation for exacerbation)
- Moderate/severe COPD exacerbations, defined as the occurrence of any of the following:[30]
    - Acute course of oral corticosteroids[31]
    - Antibiotics prescribed with a lower respiratory consultation[32]
    - COPD-related, unscheduled hospital admission / emergency department attendance (i.e. severe exacerbation)[33]

[30] Where > 1 oral corticosteroid courses / hospitalisations / antibiotic prescriptions occurred within 2 weeks of each other, they will be considered to be the result of the same exacerbation (and only counted once).

[31] Defined as any of the following: (a) courses that are definitely not maintenance therapy (defined as prescriptions for Prednisolone with daily dosing instructions of ≤ 10 mg, and for 1 mg or 2.5 mg Prednisolone tablets where daily dosing instructions are not available); (b) courses where dosing instructions suggest exacerbation treatment (e.g. 6-1 reducing, or 30 mg as directed); and (c) courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions.

[32] Identified by Read codes for any of the following: (a) lower respiratory diagnosis (including asthma, COPD and lower respiratory tract infection codes); (b) asthma/COPD review codes excluding any monitoring letter codes; (c) lung function and/or asthma monitoring codes; and (d) any additional respiratory examinations, referrals, chest x-rays, or events.

[33] Identified by Read codes for any of the following: (a) definite COPD emergency attendance or definite COPD hospital admission; (b) generic hospitalisation code which has been recorded on the same day as

- SABA reliever usage, in the year prior to the index date: average daily dose in µg/day calculated as

  ([Count of inhalers x doses in pack] / 365) x µg strength

- Lung function: FEV_1, closest to the index date: refers to the forced expiratory volume in 1 second, expressed as a percentage of the predicted normal value

- mMRC score, closest to the index date: refers to the modified British Medical Research Council questionnaire for assessing the severity of breathlessness, graded from 0, lowest score of breathlessness, to 4, highest score of breathlessness.[7] Both routine medical practice recorded and patient questionnaire mMRC scores will be used, with the most recent score taking precedence

- CCI score, calculated for the baseline period: a weighted index that takes into account the number and seriousness of comorbid diseases to estimate the risk of death from comorbid diseases[15]

- Respiratory-related therapies, in the year prior to the index date:
  - Short-acting β_2 agonist (SABA) and/or short-acting muscarinic antagonist (SAMA)
  - Long-acting β_2 agonist (LABA)
  - Long-acting muscarinic antagonist (LAMA)
  -

a lower respiratory consultation (see footnote above, refers to (a) - (c) only and excluding those where the lower respiratory code was for a lung function test only).

Appendix 3: Sample baseline results tables

		Spiromax®	Symbicort	Seretide	p-value
Age (years)	mean (SD)				
Age (categorised)	40 - 60, n (%)				
	61 - 80, n (%)				
	> 80, n (%)				
Sex	male, n (%)				
BMI (closest to index date; categorised)	non-missing, n (%)				
	underweight, n (%)				
	normal weight, n (%)				
	overweight, n (%)				
	obese, n (%)				
Smoking status (closest to index date)	non-missing, n (%)				
	non-smoker, n (%)				
	current smoker, n (%)				
	ex-smoker, n (%)				
FEV_1 % predicted (closest to index date)	non-missing, n (%)				
	median (IQR)				
FEV_1 % predicted (categorised)	< 30 (very severe), n (%)				
	30 - 49 (severe), n (%)				
	50 - 79 (moderate), n (%)				
	≥ 80 (mild), n (%)				
mMRC score (closest to index date; categorised)	non-missing, n (%)				
	0-1, n (%)				
	≥ 2, n (%)				
COPD exacerbations	median (IQR)				
COPD exacerbations (categorised)	0, n (%)				
	1, n (%)				
	2, n (%)				
	≥ 3, n (%)				
GOLD group (closest to index date)	non-missing, n (%)				
	A, n (%)				
	B, n (%)				
	C, n (%)				
	D, n (%)				
Acute oral corticosteroid courses (during baseline period)	0, n (%)				
	1, n (%)				
	2, n (%)				
	≥ 3, n (%)				

Antibiotic prescriptions (during baseline period)	0, n (%)				
	1, n (%)				
	2, n (%)				
	≥ 3, n (%)				
COPD therapy (during baseline period)	None, n (%)				
	SABA (+/- SAMA), n (%)				
	LABA, n (%)				
	LAMA, n (%)				
SABA inhaler usage (µg per day, during baseline period)	0, n (%)				
	≤ 200, n (%)				
	> 200, n (%)				
IHD (prior to index date)	n (%)				
CCI score (for baseline period; categorised)	0, n (%)				
	1 - 4, n (%)				
	5 - 9, n (%)				
	≥ 10, n (%)				

Table 6. Baseline characterisation table for Phase 1 (sample)

	Study cohorts			
	TOTAL	**Spiromax**	**Seretide**	**Symbicort**
Sample Size (n)	13,428	3,949	5,623	3,856
% Non-missing	100	100	100	100
Mean (SD)	68.63 (10.09)	68.55 (10.03)	69.28 (10.16)	67.76 (9.99)
Median (IQR)	69 (62; 76)	69 (62; 76)	70 (62; 77)	68 (61; 75)
Range:				
Minimum	40.00	40.00	40.00	40.00
Maximum	98.00	98.00	98.00	98.00

Appendix 4: OPCRD data dictionary

Patient

The Patient file contains basic patient demographics, patient registration and practice registration details.

Field Name	*Content*
Patient_ID	Anonymised patient identifier
Practice_ID	Unique practice identifier.
Year_Of_Birth	Patient year of birth in format YYYY
Gender	Patient gender
Status	Patient registration status - (R) – Registered, (L) – Left, (D) - Death
Joined_Date	Date joined practice or date first registered on database
Leaving_Date	Date left practice or date first registered on database
Leaving_Reason	Reason for leaving practice
Post_Code	"Out" part of patient postcode and first character of "in" part of patient post code

Clinical

The **Clinical** file contains medical history events. This file contains all the medical history data entered on the GP system, including symptoms, signs and diagnoses. This can be used to identify any clinical diagnoses, and deaths. Patients may have more than one row of data. The data is coded using Read codes, which allows linkage of codes to the medical terms provided.

Field Name	*Content*
Patient_ID	Anonymised patient identifier
Event_Date	Date of event
Read_Code	Five byte read code for event including terminal code if available
Read_Term	Rubric associated with read_code
Numeric_1	First numeric value if stored
Numeric_2	Second numeric value if stored
Text	First 50 characters of any text associated with entry

Referral

The **Referral** file provides details of all referrals for the defined patient cohort identified by a medical code indicating the reason for referral. This table contains information involving patient referrals to external care centres (normally to secondary care locations such as hospitals for inpatient or outpatient care).

Field Name	Content
Patient_ID	Anonymised patient identifier
Event_Date	Date of event in format dd/mm/yyyy
Read_Code	Five byte read code for event including terminal code if available
Read_Term	Rubric associated with read_code
Referral_Type	Referral type e.g. Outpatient
Referral_To	Organisation referred to
Specialism	Referral by e.g. GP referral
Attendance_Type	Attendance type e.g. First visit, follow up

Therapy

The **Therapy** file contains details of all prescriptions on the GP system. This file contains data relating to all prescriptions (for drugs and appliances) issued by the GP. Patients may have more than one row of data. Drug products and appliances are recorded by the GP using the Multilex product code system.

Field Name	*Content*
Patient_ID	Anonymised patient identifier
Event_Date	Date of event in format dd/mm/yyyy
Drug_Code	Coding for drug
Drug_Term	Drug term associated with drug code
Form	Formulation e.g. inhaler, tablets etc
Dosage	Usage instructions
Quantity	The quantity supplied
numberpack	Number of packs prescribed
Packsize	The units of quantity supplied. (the preparation)
issue_ty	Type of issue where A = Acute Issue, R = Repeat Issue
Strength	Drug strength
numberdays	Treatment days
bnf_code	BNF code

Practice

The **Practice** file contains details for practices, including region and collection information.

Field Name	*Content*
PracticeID	Unique OPC practice id
Practice_NHS	Unique NHS practice identifier.
Practice_Name	Name of practice
Practice_Address1	Address line 1
Practice_Address2	Address line 2
Practice_Address3	Address line 3
Practice_Address4	Address line 4
Practice_Postcode	Post Code
Practice_list_size	Total practice list size
Last_Extract_Date	Date when practice last did an extract

Asthma Questionnaire Data Collection

The **Asthma Questionnaire Data Collection** file contains the data collected from the questionnaires received from patients participating in the OPC Asthma Review Service. The file provides the original response as well as calculated values derived from the patient responses to the questions. Questions currently being surveyed are the following:

Questions	***Answer Options***
In the last week, how many times have you used your reliever inhaler (usually blue).	0–9; ≥10
In the last 7 days, how many days has asthma interfered with your normal activities?	0–7
In the last 7 days, how many nights have you been affected/woken by asthma symptoms (including cough)?	0–7
In the last 7 days, how many days have you experienced asthma symptoms?	0–7
In the last 4 weeks, did you miss any work, school or normal daily activity because of your asthma?	Yes; No; Unsure
In the last 4 weeks, did you wake up at night because of asthma?	Yes; No; Unsure

In the last 4 weeks, did you believe that your asthma was well controlled?	Yes; No; Unsure
In the last 4 weeks, in general, do you use an inhaler for quick relief from asthma symptoms?	Yes; No; Unsure
If yes, in the past 4 weeks, what was the highest number of puffs in 1 day you took of the inhaler?	0 / 1 to 4 puffs; 5 to 8 puffs; 9 to 12 puffs; More than 12 puffs
In the last 12 months, how many times have you needed a course of steroid tablets for worsening asthma.	0–9; ≥10
In the last 12 months, how many days have you had off work/education because of asthma.	0–9; ≥10
In the last 12 months, how many have you been admitted to hospital with breathing or chest problems?	0–9; ≥10
In the last 12 months, how many time have you been treated in accident and emergency or anywhere other than your GP surgery for your asthma?	0–9; ≥10
About smoking, which best describes you?	1 = Never smoked, 2 = Current Smoker, 3 = Ex-smoker
If you smoke or used to smoke, how many cigarettes do you/did you smoke per day?	1-5; 6-10; 11-15; 16-20; 21-30; 31-40; 41-50; >50
If you smoke, or used to smoke, how many years have you smoked/did you smoke?	1-5; 6-10; 11-15; 16-20; 21-30; 31-40; 41-50; >50
Smoking can make asthma worse - if you still smoke, would you like support from your GP or practice nurse to quit?	Yes / No
Do you have any of these symptoms: itchy, runny, blocked nose or sneezing when you don't have a cold?'	No / Occasionally & Little Bother / Occasionally & Quite a Bother / Most days & Little Bother / Most Days & a lot of bother
Do any of the following upset your asthma?	Colds / Strenuous Activity & Exercise / Allergies eg cats, dogs, pollen / Cigarette smoke
Thinking about how often you take your regular Asthma treatment during the day:	1 = I always take it exactly at the time prescribed. 2 = I occasionally miss the odd dose. 3 = I often miss or forget to take doses. 4 = I take all once a day- it's easier. 5 = I never take it.

I think my inhaler technique is very poor / I think my inhaler technique is excellent.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I do not need to take my inhaler(s) for my asthma to be well controlled / I need to take my inhalers(s) regularly for my asthma to be well controlled.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I find my inhaler(s) easy to use / I find my inhaler(s) difficult to use.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
Taking regular asthma medication does not worry me / Taking regular asthma medication worries me.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I prefer to take my asthma medications in a twice daily dose / I prefer to take my asthma medications in a once a day dose.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I use it regularly / I use it only when I feel breathless.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I never avoid using it if I can / I always avoid using it if I can.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I never forget to take it / I always forget to take it.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I never decide to miss a dose / I always decide to miss a dose.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I never choose to take it once a day / I always choose to take it once a day.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
When using preventer inhaler, do you feel a sensation at the back of the throat?	Yes / No
When using preventer inhaler, do you sometimes feel a need to cough?	Yes / No
When using preventer inhaler, do you feel your medication is deposited at the back of your throat?	Yes / No

Experience any side effects for the preventer inhaler?	Yes / No
Perceived Side Effects: Continual sore throat?	Yes / No
Perceived Side Effects: Hoarse voice?	Yes / No
Perceived Side Effects: Oral Thrush?	Yes / No
Perceived Side Effects: Abnormal Weight Gain?	Yes / No
Perceived Side Effects: Bruising?	Yes / No
Perceived Side Effects: Cough?	Yes / No
Have you had your inhaler technique checked in the last 12 months?	Yes / No
Have you seen a specialist respiratory doctor or nurse outside the practice?	Yes / No
Do you have a peak flow meter?	Yes / No
If you have a peak flow meter, please tell us your reading today?	Value
In the future, would you be willing to participate in further research?	Yes / No
Do you have a preventer inhaler?	Yes / No