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Department of Respiratory Health

Non-Interventional Study Protocol

Study Protocol Number

Historical matched-cohort study assessing whether the use of inhaled corticosteroids shortens time to first diagnosis or accelerates the progression of side effects compared to non-ICS therapies in patients with Chronic Obstructive Pulmonary Disease

(ICS use in COPD patients and risk of side effects)

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Table of contents

List of figures

N/A

List of tables

List of abbreviations

[X]	From ICD-10
ADEPT	Anonymized Data Ethics and Protocol Transparency Committee
COPD	Chronic Obstructive Pulmonary Disease
CRO	Contract Research Organization
CPRD	Clinical Practice Research Datalink
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
HbA1c	Glycated haemoglobin
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled corticosteroids
MHRA	Medicines and Healthcare products Regulatory Agency
mMRC	Modified British Medical Research Council Dyspnea Scale (mMRC)
NIHR	National Institute for Health Research
NIS	Non-Interventional Study
NEC	Not elsewhere classified
NOS	Not otherwise specified
NVS	Novartis
OCS	Oral corticosteroids
OPCRD	Optimum Patient Care Research Database
PASS	Post-Authorization Safety Study
PCOS	Polycystic ovary syndrome
QOF	Quality and Outcomes Framework
RiRL	Research in Real Life

1 Responsible parties

Not applicable (non-PASS study)

2 Abstract

Title
Historical matched-cohort study assessing whether the use of inhaled corticosteroids shortens time to first diagnosis or accelerates the progression of side effects compared to non-ICS therapies in patients with Chronic Obstructive Pulmonary Disease.

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Rationale and background
While the pharmacological treatments for COPD have evolved from the treatments for asthma, it is now known that the drugs and treatment plans required to relieve symptoms and prevent deterioration longer term are substantially different due to pathophysiological differences between the two diseases. ICS are the cornerstone of asthma pharmacologic treatment and their wide reaching benefits are well documented. In contrast, the use of ICS in COPD patients is debated given the evidence that long-term high dose exposure increases the risk of side effects.

ICS use in COPD patients has been shown to increase the risk of onset and progression of two chronic conditions that are more prevalent in older age groups: Type 2 Diabetes and osteoporosis. In a study of 388,584 patients treated for respiratory disease in Canada, current use of ICS was associated with a 34% increase in the rate of diabetes onset. This increased substantially to 64% with the highest dose of ICS. Similarly, ICS use was associated with a 34% increase in progression of diabetes, defined as first prescription of insulin among patients taking oral hypoglycemic agents, which rose to 54% with high-dose ICS therapy. Corticosteroids affect bone cells involved in the process of bone turnover, enhancing the process of bone resorption and inhibiting bone formation. As a result, studies have reported links between corticosteroids and an increased risk of developing osteoporosis. In a meta-analysis comprising 66 studies of bone density and 23 studies of fractures, strong correlations were found between cumulative dose of oral corticosteroids and loss of bone mineral density and between daily dose of oral corticosteroids and risk of fracture (van Staa et al., 2002).

Many studies have suggested that there are major discrepancies between guidelines and actual prescribing behavior of respiratory medicine. Of particular interest in the present study is the prescription of ICS above guideline recommendations. Ongoing RiRL research found that in a cohort of 11,858 patients with COPD, 19% of patients classified as GOLD group A and 28% of patients classified as GOLD group B received triple therapy (ICS+LABA+LAMA) despite

GOLD guidelines only adding ICS to recommended therapy for patients within GOLD groups C and D who are characterized as high risk. Over prescription of ICS may be due to the respiratory benefits doctors observe in patients prescribed ICS. However, physicians must weigh up the benefits of corticosteroids with the risks they pose.

Many clinical trials designed to examine the efficacy and safety of ICS use in patients with COPD consider 12 months or less of follow-up. The design to utilize all health records following index date in the present study is more appropriate to assess the relationship between ICS use and the development of chronic conditions such as Type 2 Diabetes and osteoporosis.

Research questions:

1. Does the use of ICS increase onset, shorten the time to first diagnosis or accelerate progression of Type 2 Diabetes in patients with COPD?
2. Does the use of ICS increase onset or shorten the time to first diagnosis of osteoporosis in patients with COPD?
3. Are patients with COPD taking higher daily or cumulative doses of ICS at greater risk of Type 2 Diabetes or osteoporosis compared to lower doses?
4. Does the type of corticosteroid or type of inhaler used affect the relationship between ICS use and Type 2 Diabetes or osteoporosis in patients with COPD?
5. Are patients with mild to moderate COPD prescribed ICS inappropriately in a UK primary care setting? Are side effects present in patients with mild to moderate COPD?

The overall objective of the study is to evaluate whether ICS therapy is associated with an increased onset or accelerated progression of Type 2 Diabetes, or an increased onset of osteoporosis. Firstly, these endpoints will be compared between an ICS-therapy group and non-ICS therapy group. To evaluate whether side effects are present in patients with mild to moderate COPD, the ICS therapy versus non-ICS therapy comparisons will be repeated with patients stratified by GOLD group. Subsequently, these endpoints will be analyzed within the ICS-therapy group only and compared by ICS average daily dose, ICS cumulative dose, and ICS drug and inhaler device type. In addition, overuse of ICS in COPD patients according to guidelines will be assessed.

Study design

This will be a historical, matched-cohort study assessing COPD patients from 1990 – present. For both treatment cohorts a 1-year baseline period prior to the date of first prescription of ICS therapy or first/additional prescription of non-ICS therapy (i.e. the index date) will be followed by a minimum 1-year outcome period. All of the patient's available data post index date will be utilized. Multivariable models will account for varying lengths of time at risk for side effects.

To be included in the ICS cohort, patients may switch between different types of ICS in the outcome period as long as ICS remain part of therapy. Exposure of ICS will be measured from the index date to realization of the outcome (e.g. a Type 2 Diabetes diagnosis) or from index

date to the end of the follow up period if the outcome does not occur. To be included in the non-ICS cohort, patients may be prescribed SABA, LABA, SAMA, LAMA, Methylxanthines and/or compound bronchodilator preparations and may switch between therapies in the outcome period as long as ICS are not prescribed.

Population
For patients to be included in the study, they must have clinician-diagnosed COPD, age ≥ 40 years at index date, 2 years of continuous practice records (comprising 1 year prior to index date and 1 year post index date) and ≥ 2 respiratory medication prescriptions per year of enrollment in the study. Patients must not have ICS prescriptions in baseline, clinician-diagnosed asthma, ≥ 5 oral corticosteroid prescriptions per year or an index date prior to 1st January 1990.

To be included in the progression analyses, patients must have a diagnosis prior to index date. To be included in the onset analyses, patients must not have diagnoses prior to index date.

Data sources
Secondary data will be used for this study. The study will combine anonymized medical records from patients in the Optimum Patient Care Research Database (OPCRD) and Clinical Practice Research Datalink (CPRD). The OPCRD and CPRD datasets will be constructed separately and checked for overlap, before pooling for analyses, in order to exclude patients with duplicate data. Identification of patients who are present in both OPCRD and CPRD datasets will be conducted by matching on a number of variables, such as the year of birth, gender and index date.

Both databases extract historic data so follow-up data will be available in the dataset. Diagnostic quality outcome framework (QOF) Read codes will be used which are part of the UK national quality improvement initiative and pay-for-performance scheme, ensuring good reporting of these diseases.

Data analysis

Matching process:

Initially, baseline data will be compared between unmatched cohorts. These unmatched summaries will be reviewed by the RiRL statistics team and expert clinical advisors. Members of the statistics team and expert clinical advisors will recommend the matching variables (i.e., not all variables listed in Section 7.2 will be used for matching). Patients will then be matched using direct variable mixed matching with a match maximum of 3:1 on the variables predictive of outcomes, identified by our statistics team and expert advisors, which differ between treatment groups during the baseline period, in order to minimize bias.

Patients in the non-ICS cohort will be assigned a similar index date as their matched pairs in the ICS cohort. The aim is to match +/- 1 year from index date. If exact matching reduces patient numbers drastically, +/- 2 years and +/- 3 years will be tested. Patients in the within-ICS cohort

comparisons (split by ICS average daily dose, ICS cumulative dose, corticosteroid type and inhaler device type) will not be matched.

If exact matching on other baseline demographic and clinical characteristics reduces patient numbers drastically (i.e., not representative of the overall unmatched population), consideration will be given to alternative methods to mitigate bias. These methods include regression adjustment, inverse probability of treatment weighting (IPTW) using propensity scores or propensity score adjustment (i.e., propensity score treated as continuous variable in multivariable regression analyses).

Baseline and descriptive analyses:

Summary statistics will be produced for unmatched and matched data for all baseline variables by group. Matched baseline data will be compared using conditional logistic regression.

ICS versus non-ICS comparisons:

Time to event outcomes (e.g. first diagnosis of Type 2 diabetes or osteoporosis) will be analyzed using multivariable Cox proportional hazards models with stratification on matched pairs over the follow-up time period. Regressions will be performed on the matched cohorts with different model specifications based on clinical plausibility and statistical significance of covariates. Hazard ratios, 95% confidence intervals, and p-values will be reported.

Progression of Type 2 Diabetes will be analyzed separately for each outcome in a subset of patients diagnosed with the condition prior to the index date (see Section 7.3.2 for definition of disease progression). Change in HbA1c from the one year prior to index date to 18 months post index date will be compared between ICS-initiating patients diagnosed with the condition and non-ICS initiating patients with the same condition. The rate of medication utilization per patient during an 18 month follow-up period will be compared between study groups using conditional Poisson regression, before and after adjusting for potential confounders, including baseline use of medication. Incidence rate ratios will be reported. Progression to insulin treatment will be analyzed using multivariable Cox proportional hazards models with hazard ratios reported.

Within-ICS comparisons:

The effects of ICS dosing, corticosteroid type and inhaler type on disease onset and progression will be analyzed in patients in the ICS-initiating cohort.

ICS average daily dose will be categorized during the outcome period and grouped as follows: low dose: ≤499 µg/day; medium dose: 500-999 µg/day; and high dose: ≥1,000 µg/day (fluticasone equivalents). ICS cumulative dose is the total prescribed to a patient in the outcome period and will be grouped (into low, medium and high categories) following review of the raw data. Similar analyses will be performed as described above, but using ICS average daily dose and ICS cumulative dose rather than overall ICS use as the primary explanatory variables. The

effect of corticosteroid type and inhaler type will be analyzed with similar methods as described above.

Inappropriate ICS prescribing:

Overuse of ICS in COPD patients classified as GOLD category A or B: the number of patients who are classified as GOLD category A or B with ICS prescriptions will be presented as the proportion of the total number of patients who are classified as GOLD categories A or B.

3 Amendments and updates

Not applicable (non-PASS study)

4 Milestones

Not applicable (non-PASS study)

5 Rationale and background

Chronic obstructive pulmonary disease (COPD) is a complex respiratory disease characterized by a collection of airway obstruction diseases, typically chronic bronchitis, emphysema and reactive airway disease (Mosenifar, 2014). Patients with COPD experience airway narrowing and airflow limitation associated with an enhanced chronic inflammatory response (2015a). While the pharmacological treatments for COPD have evolved from the treatments for asthma, it is now known that the drugs and treatment plans required to relieve symptoms and prevent deterioration longer term are substantially different due to pathophysiological differences between the two diseases. In contrast to the extensive requirement for inhaled corticosteroids (ICS) in the treatment of persistent asthma (Price et al., 2013, Montuschi, 2006), guidelines for COPD – including Global Initiative for Chronic Obstructive Lung Disease (GOLD) and National Institute for Health and Clinical Excellence (NICE) – only recommended adding ICS to existing therapy for patients experiencing exacerbations and severe breathlessness. GOLD guidelines introduce ICS to therapy recommendations for patients whose disease severity falls into groups C or D and whose forced expiratory volume in the first second of expiration (FEV_1) < 60% (2015a). The NICE guidelines recommend the use of ICS for patients with a FEV_1 < 50% with similarly uncontrolled symptoms (2010).

Many studies have suggested that there are major discrepancies between guidelines and actual prescribing behavior of respiratory medicine (Price et al., 2014) (in this study, comparison will be made to GOLD treatment guidelines). One study that examined patient records of 523 patients with COPD and compared their prescribed medication to the GOLD guidelines, given their symptom severity, found that 54% received less medication than the guidelines, 33% received medication according to guidelines, and 14% received more medication than the guidelines outlined. Medication prescribed correlated with health care utilization history rather than GOLD treatment guidelines (Seaman et al., 2010). Of particular interest in the present study is the prescription of ICS above guideline recommendations. Ongoing Research in Real Life (RiRL) research found that in a cohort of 11,858 patients with COPD, 19% of patients classified as GOLD group A and 28% of patients classified as GOLD group B received triple therapy (ICS+LABA+LAMA) despite GOLD guidelines only adding ICS to recommended therapy for patients within GOLD groups C and D who are characterized as high risk. In another study that evaluated the medical records of 10,711 patients with COPD, it was found that almost a fifth (18.2%) of prescriptions that included ICS were inappropriate with regards to guidelines (de Miguel-Díez et al., 2011).

Over prescription of ICS may be due to the respiratory benefits doctors observe in patients prescribed ICS. A meta-analysis of 55 primary studies, including 16,154 patients with COPD,

found that use of ICS for more than six months reduced the mean rate of exacerbations and reduced the rate of decline in quality of life (measured by the St George's Respiratory Questionnaire, SGRQ) (Yang et al., 2012). However, physicians must weigh up the benefits of corticosteroids with the risks they pose. The risks of long-term use of oral corticosteroids are well documented (2015a) but it is less clear whether ICS pose similar risks at certain doses or over certain periods of time. Long-term, high-dose ICS therapy appears to increase the incidence of systemic side effects and it has been suggested that clinical trials fail to document this due to underpowered studies with insufficient follow-up periods (Irwin and Richardson, 2006).

ICS use in COPD patients has been shown to increase the risk of onset and progression of two chronic conditions that are similarly more prevalent in older age groups: Type 2 Diabetes and osteoporosis. Corticosteroids increase the risk of diabetes as they increase insulin resistance which allows blood glucose levels to rise (Hwang and Weiss, 2014). In a study of 388,584 patients treated for respiratory disease in Canada, current use of ICS was associated with a 34% increase in the rate of diabetes onset. This increased substantially to 64% with the highest dose of ICS (equivalent to ≥1,000 µg/day of fluticasone). Similarly, ICS use was associated with a 34% increase in progression of diabetes, defined as first prescription of insulin among patients taking oral hypoglycemic agents, which rose to 54% with high-dose ICS therapy (Suissa et al., 2010a).

Ongoing RiRL work exploring the relationship between ICS use and HbA_{1c} levels in COPD patients with comorbid Type 2 Diabetes found a significant increase in the change in HbA_{1c} as cumulative dose increased (categorized as ≤40,000, 40,001-90,000 and ≥90,000 µg). When the cohort was split by drug type, it was concluded that the significant increase in HbA_{1c} with increasing cumulative doses may be driven by fluticasone propionate via metered-dose/breath-actuated inhalers, particularly at high cumulative doses. On the contrary, numerous studies have found no association between ICS and diabetes onset (O'Byrne et al., 2012, Dendukuri et al., 2002), therefore further investigation into the effects of drug type, device type and dose are required to improve understanding. Given the variation in pharmacokinetic properties between different ICS therapies, they are likely to result in distinct risks of side effects. The drugs differ in terms of oral and lung bioavailability, glucocorticoid receptor binding, and absorption rates (Herth et al., 2015, Derendorf et al., 1998, Derendorf et al., 2006).

Corticosteroids affect bone cells involved in the process of bone turnover, enhancing the process of bone resorption and inhibiting bone formation. In every bone remodeling cycle, around 30% less bone tissue is produced in patients taking corticosteroids than in normal conditions (Sewerynek and Stuss, 2012). As a result, studies have reported links between corticosteroids and an increased risk of developing osteoporosis. In a meta-analysis comprising 66 studies of bone density and 23 studies of fractures, strong correlations were found between cumulative dose of oral corticosteroids and loss of bone mineral density and between daily dose of oral corticosteroids and risk of fracture (van Staa et al., 2002). Another meta-analysis with 17,513 participants reinforced this finding, with each 500 µg increase in beclomethasone equivalents associated with a 9% increased risk of fractures (Loke et al., 2011). However, the results of the meta-analysis of 55 studies including 16,154 patients, discussed previously, demonstrated no

major effect (over a 3-year period) on bone mineral density and fractures from inhaled corticosteroids (Yang et al., 2012).

Many clinical trials designed to examine the efficacy and safety of ICS use in patients with COPD consider 12 months or less of follow-up (Herth et al., 2015). Further research using real-life data sources in populations without strict inclusion criteria, and with study lengths appropriate to the temporal development of these chronic diseases, is required to add to the literature currently available.

6 Research questions and objectives

Research questions:

1. Does the use of ICS increase onset, shorten the time to first diagnosis or accelerate progression of Type 2 Diabetes in patients with COPD?
2. Does the use of ICS increase onset or shorten the time to first diagnosis of osteoporosis in patients with COPD?
3. Are patients with COPD taking higher daily or cumulative doses of ICS at greater risk of Type 2 Diabetes or osteoporosis compared to lower doses?
4. Does the type of corticosteroid or type of inhaler used affect the relationship between ICS use and Type 2 Diabetes or osteoporosis in patients with COPD?
5. Are patients with mild to moderate COPD prescribed ICS inappropriately in a UK primary care setting? Are side effects present in patients with mild to moderate COPD?

6.1 Primary objective

The primary objective of the study is to evaluate whether ICS therapy is associated with an increased onset, shortened time to first diagnosis or accelerated progression of Type 2 Diabetes compared to non-ICS therapies.

6.2 Secondary objectives

1. To evaluate whether ICS therapy is associated with an increased onset or shortened time to first diagnosis of osteoporosis compared to non-ICS therapies.

   Further exploratory analysis:

   - Evaluate whether ICS increases risk of osteoporosis compared to non-ICS therapies.
   - Evaluate whether the effect of ICS compared to non-ICS therapies on osteoporosis outcomes is different for females as compared to males.

2. To evaluate the effects of average daily ICS dose on Type 2 Diabetes and osteoporosis. To be compared between three treatment groups. Average daily dose of ICS are fluticasone equivalents, as follows:

- Low dose: ≤499 µg/day
- Medium dose: 500-999 µg/day
- High dose: ≥1,000 µg/day

3. To evaluate the effects of cumulative dose of ICS on Type 2 Diabetes and osteoporosis. To be compared between three treatment groups. Ranges for the groups will be decided following review of the data[1].
    - Low cumulative dose
    - Medium cumulative dose
    - High cumulative dose
4. To evaluate the effects of ICS drug and inhaler device type on Type 2 Diabetes and osteoporosis. Groups for comparison will be decided following review of the data to ensure powered analyses. The following five treatment groups are proposed (subject to change):
    - Beclometasone dipropionate extrafine particle delivered by metered-dose inhaler (MDI)
    - Beclometasone dipropionate fine particle delivered by MDI
    - Budesonide delivered by dry powder inhaler (DPI)
    - Fluticasone propionate delivered by MDI
    - Fluticasone propionate delivered by DPI
5. To measure overuse of ICS in COPD patients according to guidelines. Overuse is defined as ICS prescriptions for patients in GOLD groups A and B. Patients will be categorized into GOLD groups using symptom score, lung function and risk of exacerbation data.[2] To evaluate whether side effects are present in patients with mild to moderate COPD, the ICS therapy versus non-ICS therapy comparisons will be repeated with patients stratified by GOLD group.

[1] Unlike average daily dose of ICS, for which categories are based on prescribing instructions and published literature, the amount of ICS prescribed over a five-year period is unknown and therefore setting ranges at protocol stage would be arbitrary.

[2] GOLD category A: characterized by low risk and less symptoms. Symptoms: mMRC 0-1, airflow limitation: low risk, exacerbations: ≤ 1 per year AND no hospitalization for exacerbation.
GOLD category B: characterized by low risk and more symptoms. Symptoms: mMRC ≥ 2, airflow limitation: low risk, exacerbations: ≤ 1 per year AND no hospitalization for exacerbation.
GOLD category C: characterized by high risk and less symptoms. Symptoms: mMRC 0-1, airflow limitation: high risk, exacerbations: ≥ 2 or ≥ 1 leading to hospital admission.
GOLD category D: characterized by high risk and more symptoms. Symptoms: mMRC ≥ 2, airflow limitation: high risk, exacerbations: ≥ 2 or ≥ 1 leading to hospital admission.

7 Research methods

7.1 Study design

This is a historical, matched-cohort study assessing the relationship between inhaled corticosteroids and side effects in a real-life setting. The study time period is 1990 - present. To account for changes in ICS prescribing in the study period, patients will be matched on index date to ensure they follow a similar time path. For both treatment cohorts a 1-year baseline period prior to the date of first prescription of ICS therapy or first/additional prescription of non-ICS therapy (i.e. the index date) will be followed by a minimum 1-year outcome period. All of the patient's available data post index date will be utilized. Multivariable models will account for varying lengths of time at risk for side effects. Given the requirement of 1 year of outcome data, the first prescription of ICS must occur on or before April 2015[3].

To be included in the ICS cohort, patients may switch between different types of ICS in the outcome period as long as ICS remain part of therapy. Exposure of ICS will be measured from the index date to realization of the outcome (e.g. a Type 2 Diabetes diagnosis) or from index date to the end of the follow up period if the outcome does not occur. A variable will be created, exposure time, to be used as an adjustment in all multivariable analyses. To be included in the non-ICS cohort, patients may be prescribed SABA, LABA, SAMA, LAMA, Methylxanthines and/or compound bronchodilator preparations and may switch between therapies in the outcome period as long as ICS are not prescribed (see Section 7.4.1.1 for list of drugs).

The relationship between treatment type and each side effect will be analyzed separately, there will be no combined endpoints. Patients without a diagnostic code and without treatment for Type 2 Diabetes or osteoporosis ever prior to index date will be included in the dataset for onset analysis. In patients who experience onset of the disease in the outcome period, time to diagnosis will be measured. Patients with a diagnostic code and/or treatment for Type 2 Diabetes ever prior to index date will be included in the progression analysis.

Firstly, these endpoints will be compared between an ICS therapy cohort and non-ICS therapy cohort (primary objective, secondary objective 1). These analyses will be conducted on the entire ICS and non-ICS therapy cohorts and then with the cohorts stratified by GOLD group. Subsequently, these endpoints will be analyzed within the ICS-therapy cohort only and compared by ICS average daily dose, ICS cumulative dose, and ICS drug and inhaler device type (secondary objectives 2-4). In the analysis of the effects of ICS drug type on outcomes, patients must remain on the corticosteroid for the entire outcome period. These objectives aim to clarify which aspects of ICS therapy are related to side effects.

7.2 Setting

The study will combine anonymized medical records from patients in the Optimum Patient Care Research Database (OPCRD) and Clinical Practice Research Datalink (CPRD). Both databases

[3] Assuming data extraction begins in April 2016. Amend as appropriate.

extract historic data so follow-up data will be available in the dataset. Diagnostic quality outcome framework (QOF) Read codes will be used which are part of the UK national quality improvement initiative and pay-for-performance scheme, ensuring good reporting of these diseases. See section 7.5 for further description of the databases.

The patients included in the study must fulfill all of the inclusion criteria and will be excluded if they meet any of the exclusion criteria. On data extraction, exclusion criteria will be applied sequentially and a flowchart created to show the number of patients excluded for each selection criteria.

Table 1: Inclusion and exclusion criteria – entire study

Inclusion criteria
Clinician-diagnosed COPD, recorded as a Read code, ever prior to index date
Age ≥ 40 years at index date
2 years of continuous practice records, 1 year prior to index date and 1 year post index date
≥ 2 respiratory medication prescriptions per year of enrollment in the study *ICS cohort*: ≥ 2 ICS prescriptions per year[4] *Non-ICS cohort*: ≥ 2 of any of the following per year: SABA, LABA, SAMA, LAMA, Methylxanthines and/or compound bronchodilator preparations[5]
Exclusion criteria
ICS prescriptions in the baseline
Clinician-diagnosed asthma, recorded as a Read code, ever prior to index date (except patients with an asthma resolved Read code following diagnosis)
Index date prior to 1st January 1990
≥ 5 oral corticosteroid prescriptions per year

This study is examining the relationship between ICS use and risk of side effects in a COPD population and excluding those with asthma. The rationale for excluding asthma patients is that the use of ICS in asthma treatment is not contested; inhaled corticosteroids are the cornerstone of asthma pharmacologic treatment and their wide reaching benefits are well documented (2015b). In contrast, the use of ICS in COPD patients is debated given the evidence aforementioned that long-term high dose exposure increases the risk of side effects. This is particularly concerning given COPD patients are typically older and suffer a higher number of ailments and comorbidities (Wissam et al., 2008) and studies have not observed large differences in disease outcomes with lower dose ICS compared to higher doses (Calverley et al., 2007, Anzueto et al., 2009, Sharafkhaneh et al., 2012, Szafranski et al., 2003).

[4] Patients may switch between different types of ICS in the outcome period as long as ICS remain part of therapy.

[5] Either ≥2 repeat prescriptions of the same class of drug or ≥2 prescriptions of different classes of drug. Patients may switch between therapies in the outcome period as long as ICS are not prescribed.

In addition to the criteria stated above for inclusion in the study, patients eligible for inclusion in the analysis of onset or progression of side effects are described in Tables 2-4.

Table 2: Inclusion and exclusion criteria – Type 2 Diabetes progression analysis

Inclusion criteria
Clinician-diagnosed Type 2 Diabetes, recorded as a Read code, and/or antidiabetic medication and/or ≥ 2 HbA1c readings > 6.5% ever prior to index date
≥ 1 HbA1c reading in the year prior to index date
≥ 1 HbA1c reading in period 20 days to 18 months post index date
Exclusion criteria
Diabetes resolved code, recorded as a Read code, following the diagnostic code
Clinician-diagnosed Type 1 Diabetes, recorded as a Read code, ever prior to index date
Clinician-diagnosed PCOS, recorded as a Read code, and ≥1 Metformin prescriptions ever prior to index date

Table 3: Exclusion criteria – Type 2 Diabetes onset analysis

Exclusion criteria
Clinician-diagnosed Type 2 Diabetes, recorded as a Read code, and/or antidiabetic medication and/or ≥ 2 HbA1c readings > 6.5% ever prior to index date
Clinician-diagnosed Type 1 Diabetes, recorded as a Read code, ever prior to index date
Clinician-diagnosed PCOS, recorded as a Read code, and ≥ 1 Metformin prescriptions in the outcome period

Table 4: Exclusion criteria – Osteoporosis onset analysis

Exclusion criteria
Clinician-diagnosed osteoporosis, recorded as a Read code, ever prior to index date

Initially, baseline data will be compared between unmatched cohorts. These unmatched summaries will be reviewed by the RiRL statistics team and clinical advisors. Members of the statistics team and clinical advisors will recommend the matching variables (i.e. not all variables listed below will be used for matching). Patients will then be matched using direct variable mixed matching with a match maximum of 3:1 on the variables predictive of outcomes, identified by our statistics team and clinical advisors, which differ between treatment groups during the baseline period, in order to minimize bias.

Mixed matching is a process that will help utilize more of the data by matching non-ICS patients (smaller cohort) to varying numbers of ICS patients (larger cohort). In other words, there will

be a cohort of unique patients matched 1:1, another cohort of unique patients matched 1:2, and a third cohort of unique patients matched 1:3. The analysis will be conducted using all of the matched patients even though some patients have 1 match while other patients may have 3 matches. A sensitivity analysis will be performed to analyze only the unique cohort of 1:3 matched patients and compare the results to the cohort of all patients.

Patients will be matched on index date[6], the date of first prescription of ICS for the ICS cohort, so that the non-ICS cohort follow a similar time path to their matched pair.

Variables that may be matched are:

- Demographic characteristics such as sex, age, BMI category and smoking status
- COPD severity/treatment factors:
    - Symptom score: Modified British Medical Research Council Dyspnea Scale (mMRC)
    - Lung function: FEV_1 percent predicted
    - Number of moderate/severe COPD exacerbations
- Corticosteroid exposure other than those inhaled for the lungs[7] such as inhaled nasal corticosteroid prescriptions
- Comorbidities:
    - Cardiovascular disease
    - Ischemic heart disease
    - Hypertension
    - Cancer
    - Charlson Comorbidity Index score[8]

7.3 Endpoints

7.3.1 Type 2 Diabetes onset

First, Type 2 Diabetes onset and time to first diagnosis will be compared between the ICS cohort and non-ICS cohort. Then, it will be compared between the ICS and non-ICS cohorts stratified by GOLD group. Finally, it will be compared solely in the ICS cohort with patients categorized

[6] Aim to match +/- 1 year from index date. If exact matching reduces patient numbers drastically, +/- 2 years and +/- 3 years will be tested. The time frame is dependent on prescribing pattern changes or guideline recommendations during the outcome period.

[7] The analyses will be adjusted for oral corticosteroid prescriptions.

[8] The Charlson comorbidity index predicts the ten-year mortality for a patient who may have a range of comorbid conditions. Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one. Age is also considered, with older ages assigned higher scores. Scores are summed to provide a total score to predict mortality (Moses, 2014).

according to ICS average daily dose, ICS cumulative dose, corticosteroid type, inhaler device type, and interaction between corticosteroid type and inhaler device type.

Type 2 Diabetes onset is defined in this study as a diagnostic Read code for Type 2 Diabetes, and/or antidiabetic drug prescriptions and/or ≥ 2 HbA1c readings > 6.5%. Given the use of Metformin for polycystic ovary syndrome (PCOS) treatment, patients with a diagnosis of PCOS and ≥ 1 Metformin prescriptions in the outcome period will be excluded from the analysis.

To analyze onset of Type 2 Diabetes, the difference in the proportion of patients with a first diagnosis in the outcome period will be compared between groups. Then, survival analysis methods will be used to compare the difference in time to first diagnosis of Type 2 Diabetes between groups.

7.3.2 Type 2 Diabetes worsening disease control & disease progression

First, Type 2 Diabetes worsening disease control and disease progression will be compared between the ICS cohort and non-ICS cohort. Then, it will be compared between the ICS and non-ICS cohorts stratified by GOLD group. Finally, it will be compared solely in the ICS cohort with patients categorized according to ICS average daily dose, ICS cumulative dose, corticosteroid type, inhaler device type, and interaction between corticosteroid type and inhaler device type.

Type 2 Diabetes worsening disease control and disease progression will be analyzed in the group of patients who have a diagnostic Read code for Type 2 Diabetes, and/or antidiabetic drug prescriptions and/or ≥ 2 HbA1c readings > 6.5% ever prior to index date.

Worsening disease control will be measured by change in blood glucose level defined as increased glycated haemoglobin (HbA1c) readings. HbA1c changes of 0.5% and higher will be considered a clinically significant change (NGSP, 2011, Little et al., 2011). Caution must be taken when drawing conclusions regarding HbA1c change given the impact of behavioral factors such as diet and medication adherence on the readings. In order to minimize the effects of external factors and measure the effect of ICS use on glycaemic control as closely as possible, the HbA1c value closest prior to index date will be compared to the first reading after 20 days post index date. The maximum period for inclusion of an HbA1c value will be 18 months post index date.

Disease progression will be measured by treatment change[9]:

- Addition of antidiabetic medication: antidiabetic medication will be categorized as 0, 1, 2, ≥ 3 non-insulin, and insulin (+/- other), and analyzed separately as count of medications per patient per year in the outcome period.
- Progression of ongoing diabetes treatment to insulin: time between index date and first prescription of insulin in outcome period.

[9] Dose increases will not be considered as progression of disease as often doctors will begin patients on low doses of new medication at first, gradually increasing the dose to lower the chance of side effects.

7.3.3 Osteoporosis onset

First, osteoporosis onset will be compared between the ICS cohort and non-ICS cohort. Then, it will be compared between the ICS and non-ICS cohorts stratified by GOLD group. Finally, it will be compared solely in the ICS cohort with patients categorized according to ICS average daily dose, ICS cumulative dose, corticosteroid type, inhaler device type, and interaction between corticosteroid type and inhaler device type.

Osteoporosis onset is defined in this study as a diagnostic Read code for osteoporosis. Osteoporosis drug prescriptions without an accompanying diagnosis code will not be considered indicative of osteoporosis presence given commonly prescribed osteoporosis drugs are prescribed for other conditions (e.g. Bisphosphonates for patients with Paget's disease, bone metastasis or multiple myeloma and Strontium for patients with certain forms of cancer) and are used for osteopenia.

To analyze onset of osteoporosis, difference in proportion of patients with a first diagnosis in the outcome period will be compared between groups. Then, survival analysis methods will be used to compare the difference in time to diagnosis of osteoporosis between groups.

To evaluate the effect of ICS on osteoporosis outcomes by gender, additional osteoporosis onset analyses will be completed with the cohort stratified by gender.

Further **exploratory analysis**: to evaluate whether ICS increases risk of osteoporosis compared to non-ICS therapies. Increased risk is defined as prescriptions of vitamin D and calcium (such as Adcal-D3) without a diagnosis of osteoporosis. The combination of vitamin D and calcium is prescribed as a preventative treatment for patients considered to be high risk for osteoporosis and fractures (Compston et al., 2014). To analyze increased risk of osteoporosis, difference in proportion of patients with combined vitamin D and calcium prescriptions in the outcome period will be compared between the ICS and non-ICS cohort.

7.3.4 Overuse of ICS

Overuse is defined as ICS prescriptions for patients in GOLD groups A and B. Number of patients who are classified as GOLD category A or B with ICS prescriptions will be presented as a proportion of the total number of patients who are classified as GOLD categories A or B.

7.4 Variables

7.4.1 Inclusion and exclusion criteria

- Diagnosis of COPD ever prior to index date (Read codes)
- Diagnosis of asthma ever prior to index date (Read codes)
- Clinician assigned asthma resolved ever prior to index date (Read codes)
- Index date

- Age at index date (in years)
- Diagnosis of Type 2 Diabetes ever prior to index date and in outcome period (Read codes)
- Clinician assigned diabetes resolved ever prior to index date (Read codes)
- Diagnosis of Type 1 Diabetes ever prior to index date (Read codes)
- Number of and type of antidiabetic medication prescriptions ever prior to index date and in outcome period (Read codes)
- Diagnosis of polycystic ovary syndrome every prior to index date and in the outcome period (Read codes)
- Date of and result of HbA1c readings ever prior to index date and in the period 20 days to 18 months post index date (Read codes)
- Diagnosis of osteoporosis ever prior to index date (Read codes)

7.4.1.1 Respiratory treatment

- Number of prescriptions of the following per year of the study period (minimum 2 years total, 1 year prior to and 1 year post index date)
    - Corticosteroids:
        - ICS monotherapy or combination therapy including any of the following:
            - Beclometasone Dipropionate
            - Budesonide
            - Ciclesonide
            - Fluticasone Propionate
            - Fluticasone Furoate
            - Mometasone Furoate
        - OCS
            - Prednisolone
            - Prednisone
            - Methylprednisolone
            - Dexamethasone
            - Hydrocortisone
    - Drugs forming the ‘non-ICS’ group are as follows:
        - SABA
            - Salbutamol

- Terbutaline Sulfate
- Isoproterenol

- LABA
  - Formoterol Fumarate
  - Salmeterol
  - Indacaterol
  - Olodaterol
  - Bambuterol Hydrochloride
  - Vilanterol
- SAMA
  - Ipratropium Bromide
- LAMA
  - Tiotropium
  - Glycopyrronium
  - Aclidinium Bromide
  - Umeclidinium
- Methylxanthines
  - Theophyllines
  - Dyphylline
  - Oxtriphylline
  - Aminophylline
- Phosphodiesterase-4 inhibitor
  - Roflumilast
- Compound bronchodilator preparations
  - Ipratropium bromide/Salbutamol & Ipratropium bromide/Albutamol
  - Umeclidinium/Vilanterol
  - Indacaterol/Glycopyrronium
  - Aclidinium Bromide/Formoterol Fumarate

7.4.2 Patient demographics/baseline characterization

- Patient demographics:

- Age at index date (in years)
- Sex (male/female)
- Smoking status (Read code closest to and within 5 years prior to index date and categorized as non-smoker, current smoker and ex-smoker)
- BMI[10] (calculated from height and weight data if available[11] and taken from practice recorded BMI value if not, within 10 years prior to index date)

- Number of antibiotic prescriptions in the year prior to index date (Read codes)
- Number of oral corticosteroid prescriptions in the year prior to index date (Read codes)
- COPD severity/treatment factors
  - Duration of COPD, measured from first diagnostic COPD Read code to most recent data extraction (in years)
  - Percent predicted FEV_1 (taken from practice recorded value if available or calculated from FEV_1 value if not, within 5 years prior to index date)
  - Moderate and severe COPD exacerbations (in year prior to index date, defined as occurrence of COPD-related unscheduled hospital admission or A&E attendance; OR prescription of acute course of oral corticosteroids; OR prescription of antibiotic on the same day as a lower respiratory consultation)[12]
  - mMRC score taken from medical records (recorded closest to and within 5 years prior to index date)
  - GOLD group categorized: A, B, C or D. Calculated using FEV1, exacerbations and mMRC data (recorded closest to and within 5 years prior to index date)
- Corticosteroid exposure (other than those inhaled for the lungs)
  - Nasal corticosteroid prescriptions in the year prior to index date (Read codes, BNF section 12.2.1)

[10] Categorized as underweight <18.5, normal weight ≥18.5 and <25, overweight ≥25 and <30, obese ≥30

[11] Weight (kg) divided by height (metres) squared

[12] Where ≥1 oral steroid course / hospitalization / antibiotics prescription occur within 2 weeks of each other, these events will be considered to be the result of the same exacerbation (and will only be counted once). COPD-related hospitalizations: consist of either a definite COPD A&E attendance or a definite COPD hospital admission; OR a generic hospitalization 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). Lower respiratory consultations consist of the following: (a) lower respiratory Read codes (including asthma, COPD and LRTI read codes); (b) asthma/COPD review codes excluding any monitoring letter codes; (c) lung function and/or asthma monitoring; (d) any additional respiratory examinations, referrals, chest x-rays, or events. Acute oral steroid use associated with COPD exacerbation treatment will be defined as: all courses that are definitely not maintenance therapy, and/or all courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed), and/or all courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions (where "maintenance therapy" is defined as: daily dosing instructions of <=10mg Prednisolone or prescriptions for 1mg or 2.5mg Prednisolone tablets where daily dosing instructions are not available).

- History of comorbidities:
    - Cardiovascular disease diagnosis ever prior to index date (Read codes)
    - Ischemic heart disease diagnosis ever prior to index date (Read codes)
    - Hypertension diagnosis ever prior to index date (Read codes)
    - Cancer (any form) diagnosis ever prior to index date (Read codes)
    - Charlson Comorbidity Index Score: based on diagnoses ever prior to index date (Read codes)

7.4.3 Variables used in the outcome analysis

- Gender (male/female)
- GOLD group categorized: A, B, C or D (recorded closest to and within 5 years prior to index date)
- Treatments for COPD
    - ICS prescriptions in the outcome period (see Section 7.4.1.1) (Read codes)
        - Categorized by corticosteroid type
        - Categorized by inhaler type: metered-dose inhaler, dry powder inhaler
    - All non-ICS prescriptions in the outcome period (see Section 7.4.1.1) (Read codes)
    - Average ICS mcg daily dose in the outcome period categorized: low dose ≤499 µg/day, medium dose 500-999 µg/day, and high dose ≥1,000 µg/day (Fluticasone equivalents). Calculated as: ∑(((Count of inhalers x doses in pack) / baseline period) x mcg strength)
    - Cumulative ICS prescribed in the outcome period. Cumulative dose is the total prescribed in the outcome period, considering number of prescriptions, the dose and potency of the ICS. Calculated as: ∑((Count of inhalers x doses in pack) x mcg strength)
- Type 2 Diabetes onset
    - Type 2 Diabetes diagnostic code in outcome period (Read codes)
    - Antidiabetic medication prescriptions in outcome period (Read codes)
    - HbA1c readings greater than 6.5% in outcome period (Read code)
    - Time (in days) between index date and first Type 2 Diabetes onset indicator
- Type 2 Diabetes worsening disease control & progression
    - Type 2 Diabetes diagnostic code ever prior to index date (Read codes)
    - Antidiabetic medication prescriptions ever prior to index date (Read codes)
    - HbA1c readings in year prior to index date (Read codes)

- HbA1c readings in the period 20 days to 18 months post index date (Read codes)
- Antidiabetic medication prescriptions in the outcome period categorized as: 0, 1, 2, ≥ 3 non-insulin, and insulin +/- other
- Insulin prescriptions ever prior to index date (Read codes)
- Number of patients who progressed from antidiabetic medication to insulin in the outcome period (Read codes)
- Time (in days) between index date and first prescription of insulin treatment in the outcome period (Read codes)

- Osteoporosis onset & risk of osteoporosis
  - Osteoporosis diagnostic code in outcome period (Read codes)
  - Time (in days) between index date and first osteoporosis diagnosis Read code
  - Combined vitamin D and calcium prescriptions in the outcome period (Read codes)
- Confounding variables
  - Number of oral corticosteroid prescriptions per year of the outcome period (Read codes)
  - Number of oral corticosteroid prescriptions overall in the outcome period (Read codes)
  - Length of outcome period (in years)
  - Duration of medication-treated Type 2 Diabetes (in years)
  - Diabetic treatment change (binary outcome yes/no). Measured from baseline to 18 months following index date and only considered if the change occurs prior to the outcome HbA1c measurement. Antidiabetic medication prescriptions are categorized as: 0, 1, 2, ≥ 3 non-insulin, and insulin +/- other. Any change within this categorization from baseline to outcome period aforementioned will be classified as diabetic treatment change.

7.5 Data sources

Secondary data will be used for this study. Data from the CPRD and OPCRD will be combined. The data will be retrieved from the CPRD provided by the UK Department of Health and from the OPCRD provided by Optimum Patient Care. The designated contract research organization, Research in Real Life, will perform the analysis according to the contract agreement.

The rationale for combining CPRD and OPCRD datasets is to increase the number of patients to be included in the studies and therefore increase the power we have to detect clinically relevant differences between groups. Therefore, as the study includes subgroup analyses and matching, we would like to maximize the pool of patients available in order to retain sufficient patients once these processes are conducted. OPCRD and CPRD data have been combined in

multiple previous studies conducted by RiRL, including most recently, Price, et al., 2015, Israel, et al., 2015 and Roche, et al., 2015.

The CPRD is a large computerized primary care database. The CPRD contains de-identified, longitudinal data from 5 million active medical records from more than 600 subscribing practices throughout the UK. A practice-based quality marker, the "up-to-standard date", is generated by the CPRD for each subscribing practice and data subsequent to the practice up-to-standard date are considered to be acceptable, research quality, prospectively recorded data. The CPRD is well-validated and used frequently for medical and health research.

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 2.4 million patients from over 525 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 OPCRD and CPRD datasets will be constructed separately and checked for overlap, before pooling for analyses, in order to exclude patients with duplicate data. Identification of patients who are present in both OPCRD and CPRD datasets will be conducted by matching on a number of variables, such as the year of birth, gender and index date. During this process patients will never become identifiable and the data analysts from RiRL, who will construct the datasets, have no access to any data in a patient identifiable form. From pooling of data from these two databases for previous studies conducted by RiRL, we observed between 2-4% overlap and we have no reason to expect the percentage overlap to be different in this instance.

The source data for each patient will be the same for both datasets (electronic records extracted from primary care practices) in the form of patient IDs, event dates and Read codes. Once data is received from OPCRD and CPRD, variables will be built from this raw data using algorithms and lists of codes constructed to identify certain diagnoses/drugs. The same variables will be constructed for the data from each dataset. Due to different extraction techniques and information governance rules between OPCRD and CPRD, the data contained in each dataset may differ slightly for some of the patients who are present in both OPCRD and CPRD. The majority of patients will only appear in one of the datasets and so we will use data from whichever dataset they appear in. In cases where we identify a patient as existing in both datasets, we propose to keep data for the patient from the dataset in which the patient has the least amount of missing data with respect to key variables (variables list in Section 7.4). If patients have the same amount of data with respect to key variables in both datasets, we will

keep data for the patient from the dataset in which the patient has the least amount of missing data with respect to all variables required for the study.

CPRD data will be linked to Hospital Episode Statistics (HES) to identify hospital-related events. HES data will be used where applicable, as in general they provide more complete and reliable detailed information on emergency room attendances, inpatient hospitalizations and outpatient attendances than GP records. Analyses requiring information on hospital-related events will be performed in a subgroup of patients from CPRD who have HES data available.

7.6 Data management

Data preparation and exploratory data analysis will be performed for variables in the dataset before any outcomes analysis. This enables variables to be checked, for example, for validity of data, missing data and outliers (which will be checked and inaccurately coded data labelled as missing). Skewed data will be transformed or categorized, as appropriate. In analyses, a 'missing' category is assigned to missing data and analyzed so that patients are not removed from analysis.

See details in section 7.5 on the construction of the datasets.

7.7 Data analysis

All analyses will be performed by Research in Real Life and Cambridge Research Support Ltd.

All statistical analyses will be conducted using Microsoft Office Excel 2013 (Microsoft, Bellevue, WA), IBM SPSS Statistics version 23 (SPSS Statistics; IBM, Somers, NY), Stata SE version 14 (StataCorp, College Station, TX) and SAS version 9.4 (SAS Institute, Cary, NC). Statistically significant results will be defined as $p < 0.05$.

7.7.1 Matching process

Initially, baseline data will be compared between unmatched cohorts. Specifically, statistical comparisons (e.g., chi-squared, Mann-Whitney U tests, etc.) of demographic and clinical characteristics between ICS and non-ICS cohorts will be employed to aid in the process of variable selection for matching. These unmatched summaries will be reviewed by the RiRL statistics team and expert clinical advisors. Members of the statistics team and expert clinical advisors will recommend the matching variables (i.e., not all variables listed in Section 7.2 will be used for matching). Patients will then be matched using direct variable mixed matching with a match maximum of 3:1 on the variables predictive of outcomes, identified by our statistics team and expert advisors, which differ between treatment groups during the baseline period, in order to minimize bias. Mixed matching is a process that will help utilize more of the data by matching non-ICS patients (smaller cohort) to varying numbers of ICS patients (larger cohort). In other words, there will be a cohort of unique patients matched 1:1, another cohort of unique patients matched 1:2, and a third cohort of unique patients matched 1:3. The analysis will be conducted using all of the matched patients even though some patients have 1 match while other patients may have 3 matches. A sensitivity analysis will be performed to analyze only the unique cohort of 1:3 matched patients and compare the results to the cohort of all patients.

Once ICS and non-ICS cohorts are matched using mixed matching, balance between groups will be assessed using two methods: (1) comparing p-values using a conditional logistic regression with significant at $p<0.05$; and (2) standardized differences to compare baseline prevalence and means with balance considered achieved if absolute differences are within + or - 10%.

If exact matching on other baseline demographic and clinical characteristics reduces patient numbers drastically (i.e., not representative of the overall unmatched population), consideration will be given to alternative methods to mitigate bias. These methods include regression adjustment, inverse probability of treatment weighting (IPTW) using propensity scores or propensity score adjustment (i.e., propensity score treated as continuous variable in multivariable regression analyses).

Patients in the within-ICS cohort comparisons (split by ICS average daily dose, ICS cumulative dose, corticosteroid type and inhaler device type) will not be matched to non-ICS cohort patients or within-ICS cohort patients. Regression adjustment will be the primary method to mitigate bias in the within-ICS cohort patient group. However, alternative methods such as direct matching between low vs. medium vs. high dose ICS groups, propensity score adjustment or IPTW may be considered if expert clinical advisors determine the within-ICS cohort analysis is vunerable to confounding by indication even after regression adjustment.

7.7.2 Baseline characterization

Summary statistics will be produced for unmatched and matched data for all baseline variables by group. Results will be reported as:

- Variables measured on the interval/ratio scale:
    - Sample size (n) and percentage of non-missing patients
    - Mean and variance/standard deviation (SD)
    - Median and inter-quartile range (IQR) (25^{th} and 75^{th} percentiles)
- Categorical Variables:
    - Sample size (n)
    - Count and percentage by category (distribution)

For unmatched baseline data, groups will be compared using the following tests:

- Variables measured on the interval/ratio scale:
    - Independent samples t-test/ paired t-test
    - Mann-Whitney U test (skewed data)
- Categorical Variables:
    - Chi-square test

Matched baseline data will be compared using conditional logistic regression.

7.7.3 Corticosteroid exposure

To be included in the ICS cohort, patients may switch between different types of ICS in the outcome period as long as ICS remain part of therapy. Exposure of ICS will be measured from the index date to realization of the outcome (e.g. a Type 2 Diabetes diagnosis) or from index date to the end of each patient's follow up period if the outcome does not occur.

Additionally, multivariable models will be adjusted for time-varying OCS use in each cohort. OCS will be categorized as the number of prescriptions per patient per year during the one-year baseline period, each year during the follow-up period for the onset analyses, and the total number of OCS prescriptions over each patients' follow-up period. For progression analyses, OCS will be categorized as the number of prescriptions per patient per year during the one-year baseline period and the total number during the 18-month follow-up period.

7.7.4 Analysis of Type 2 Diabetes outcomes

Outcome analysis will be performed after the matching process. Unadjusted comparisons of event rates for diabetes onset will be compared between matched groups using Kaplan-Meier curves. Annualized event rates for diagnoses of diabetes will be calculated by the number of newly diagnosed patients divided by the total number of person years of follow-up for each group. Outcome results will be presented for the first year of follow-up and for the total follow-up time.

Type 2 Diabetes time to first diagnosis will be analyzed using a multivariable Cox proportional hazards models over the follow-up time period. The first initiation of ICS will be the index date, and serve as the analytic start time for the analysis. Patients that meet the inclusion criteria will be followed until the first diagnosis or prescription for diabetes, death, or until the end of their follow-up period. Varying follow-up time periods will be addressed in the multivariable regression models. Regressions will be performed on the matched cohorts with different model specifications based on clinical plausibility and statistical significance of covariates. Hazard ratios, 95% confidence intervals, and p-values will be reported. Censoring (i.e., observation is terminated before an individual experiences a diagnosis) may occur in this analysis in the following cases: (a) a patient has not experienced a diagnosis by the end of the observation time; (b) a patient dies before the observation time ends.

Diabetes progression will be analyzed separately for each outcome in a subset of patients diagnosed with diabetes prior to the index date. Change in HbA1c from the one year prior to index date to 18 months post index date will be compared between ICS-initiating patients diagnosed with diabetes and non-ICS initiating patients with diabetes. Antidiabetic medication utilization and progression to insulin treatment will be compared during the 18 month follow-up period between ICS-initiating patients diagnosed with diabetes and non-ICS initiating patients with diabetes.

- Change in HbA1c: change in HbA1c for each patient will be calculated as the difference between baseline (nearest to index date prior to ICS diagnosis) and first HbA1c value after 20 days post index date. The maximum period for inclusion of an HbA1c value will be 18 months post index date. Mean change in HbA1c (%) from baseline to follow-up will be compared between the study groups using a paired t-test. Further adjusted analyses using generalized estimating equations will account for correlation between matched patients, observations over time and confounders including diabetic treatment change in the months prior to follow-up HbA1c measurement. Mean change in HbA1c (%) and 95% confidence intervals between study groups will be reported.
- Antidiabetic medication utilization: The rate of prescribed antidiabetic medications per patient during an 18 month follow-up period will be compared between study groups using conditional Poisson regression, before and after adjusting for potential confounders including baseline use of antidiabetic medication. Incidence rate ratios, 95% confidence intervals, and p-values will be reported.
- Progression to insulin treatment: Using a subset of patients not using insulin prior to the index date (within the subgroup of patients diagnosed diabetes prior to index date), the time to first prescription of insulin within 18 months post index date will be estimated using a multivariable Cox proportional hazards model with stratification on matched pairs. Hazard ratios, 95% confidence intervals, and p-values will be reported.

The analyses above will be repeated with patients stratified by GOLD group to analyze side effects in patients inappropriately prescribed ICS.

7.7.5 Analysis of osteoporosis outcomes

Time to onset of osteoporosis will be analyzed using a similar approach as described in the Type 2 Diabetes analysis section. Specifically, the analysis will employ multivariable Cox proportional hazards models with stratification on matched pairs over the follow-up period. The first initiation of ICS will be the index date, and serve as the analytic start time for the analysis. Patients that meet the inclusion criteria will be followed until the first diagnosis or prescription for osteoporosis, death, or until the end of their follow-up period. Regressions will be performed on the matched cohorts with different model specifications based on clinical plausibility and statistical significance of covariates. Hazard ratios, 95% confidence intervals, and p-values will be reported.

The analyses above will be repeated on stratified unmatched samples of females and males separately to assess differences in the effect of ICS on osteoporosis outcomes by gender. Additionally, analyses will be repeated with patients stratified by GOLD group to analyze side effects in patients inappropriately prescribed ICS.

An exploratory analysis will evaluate whether ICS increases risk of osteoporosis compared to non-ICS therapies. Increased risk is defined as prescriptions of vitamin D and calcium (such as Adcal-D3) without a diagnosis of osteoporosis. To analyze increased risk of osteoporosis, the frequency (%) of patients with combined vitamin D and calcium prescriptions in the outcome

period will be compared between the ICS and non-ICS cohort using a 2 x 2 table with a chi-square test for association.

7.7.6 Within-ICS cohort comparisons

Effects of ICS dosing, corticosteroid type and inhaler type on disease onset and progression within ICS-initiating cohort: additional analyses for both primary (e.g. diabetes onset and progression) and secondary endpoint (e.g. osteoporosis onset) will be conducted, focusing on patients in the ICS-initiating cohort.

ICS average daily dose will be categorized during the outcome period following the index date and grouped as follows: low dose: ≤499 µg/day; medium dose: 500-999 µg/day; and high dose: ≥1,000 µg/day (fluticasone equivalents). ICS cumulative dose is the total prescribed to a patient in the outcome period and will be grouped (into low, medium and high categories) following review of the raw data. Similar analyses will be performed as described above, but using ICS average daily dose and ICS cumulative dose rather than overall ICS use as the primary explanatory variables. The effect of corticosteroid and inhaler type will be analyzed with similar methods as described above.

7.7.7 Overuse of ICS

Overuse of ICS in COPD patients classified as GOLD category A or B: the number of patients who are classified as GOLD category A or B with ICS prescriptions will be presented as the proportion of the total number of patients who are classified as GOLD categories A or B.

7.8 Quality control

Read code lists will be reviewed by RiRL's clinical advisers and Novartis. Where possible and appropriate QOF Read code lists will be used which are part of the UK national quality improvement initiative and pay-for-performance scheme codes. The statistical programming performed to generate the results will be archived with all the documentation relating to the project on RiRL's internal systems.

7.9 Limitations of the research methods

The data comes from an existing database, which means that the time points at which measurements are taken are not controlled, but are simply in line with the usual course of treatment of the patient. The datasets represent information collected for clinical and routine use rather than specifically for research purposes. Although extensive quality control and validity checks are conducted on the practice level, the validity and completeness of individual patient records cannot be assessed.

As the data source selected for this study is a primary care database it is likely that there will be missing data, where certain variables were not recorded in the course of routine care. We will report the percentage of missing data to show the representativeness of the summary statistics.

However, missing data should not be a major issue, because baseline characteristics, such as age, sex and all comorbidities, are reliably recorded by GPs in primary care databases.

The data source does not have dispensing data or information regarding actual use of medicine so the ICS average daily dose and cumulative dose variables are informed by prescriptions alone. Like all database adherence studies, we will assume that prescriptions were dispensed and used as indicated.

The possibility of OCS use in the 'non-ICS' cohort is a limitation of the study design. Extensive consideration was given to this factor. However, we do not wish to exclude patients who are prescribed OCS courses from the non-ICS cohort because this would exclude patients with exacerbations and make this a less-severe COPD group than the ICS group. The number of OCS prescriptions per year of the outcome period and overall prescriptions in the outcome period will be accounted for in the analysis. Patients with long term use, ≥5 OCS prescriptions in a year, have been removed from the study population.

7.10 Other aspects

Not applicable

8 Protection of human subjects

OPCRD is a non-profit social enterprise and its use for research purposes has approval from the NHS Health Research Authority and is governed by the ADEPT Committee. The data is anonymized and extracted as IG-Compliant data extractions primary care practices.

CPRD is a governmental, not-for-profit research service, jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA), a part of the Department of Health. They provide anonymized primary care records for public health research.

9 Management and reporting of adverse events/adverse reactions

As this is a study based on secondary use of data, safety monitoring and safety reporting, where there is a safety relevant result, is provided on an aggregate level only; no reporting on an individual case level is required. In studies based on secondary use of data with a safety relevant result, reports of adverse events/adverse reactions should be summarized in the study report, i.e. the overall association between an exposure and an outcome. Relevant findings from the study report will be included in the periodic aggregated regulatory reports submitted to Health Authorities.

10 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of

results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

11 Read codes

Read code lists are available upon request in Excel format. Please email Rosie McDonald at rosie@rirl.org to request any list from the variables in Section 7.4.

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