**Non-Interventional Study Protocol**

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# Burden of disease in patients with COPD and high blood eosinophil counts

An observational historical follow-up study to evaluate the burden of disease in patients with COPD who have high blood eosinophil counts

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# LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| A&E | Accident and Emergency |
| AIC | Akaike's Information Criterion |
| AZ | AstraZeneca |
| BDP | Beclomethasone Dipropionate |
| BTS/SIGN | British Thoracic Society / Scottish Intercollegiate Guidelines Network |
| CFC | Chlorofluorocarbon |
| CI | Confidence Interval |
| COPD | Chronic Obstructive Pulmonary Disease |
| $FEV_1$ | Forced Expiratory Volume in the first second |
| HES | Hospital Episode Statistics |
| HR | Hazard Ratio |
| HRU | Health care Resource Use |
| ICD | International Classification of Diseases |
| ICS | Inhaled Corticosteroids |
| ID | Index date |
| LABA | Long-Acting Beta Agonist |
| LTRA | Leukotriene Receptor Antagonist |
| MPR | Medication Possession Ratio |
| mMRC | Modified Medical Research Council Score |
| NHS | National Health Service |
| OPCRD | Optimum Patient Care Research Database |
| OPRI | Observational and Pragmatic Research Institute |
| RR | Rate Ratio |
| SABA | Short-Acting Beta Agonist |
| SC | Steering Committee |
| SD | Standard Deviation |
| UK | United Kingdom |

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# PROTOCOL SYNOPSIS

## Burden of disease in patients with COPD and high blood eosinophil counts

An observational historical follow-up study to evaluate the burden of disease in patients with COPD who have high blood eosinophil counts

**Background/Rationale:**

Eosinophilic inflammation is thought to be a characteristic feature of asthma rather than chronic obstructive pulmonary disease (COPD). However, studies have shown that there is a subset of COPD patients with eosinophilic airway inflammation, even after exclusion of patients with any features of asthma (1).

Previous work conducted at OPRI found an increased risk of exacerbations with high blood eosinophil counts in patients with COPD who were not actively smoking. However, the role of different treatment regimens in the association between blood eosinophil count and COPD exacerbations needs to be further elucidated. It is unknown whether the association is also present in patients who are adherent to ICS and in patients on triple therapy to which one third of UK patients with COPD progresses in real life (2).

COPD is associated with high mortality and morbidity. Hospitalizations for acute exacerbations of COPD account for a relatively large proportion of annual direct costs for COPD (3). Furthermore, one in five patients is estimated to require re-hospitalization within 30 days of discharge after an admission for acute exacerbation, indicating a lack of effectiveness of standard treatment to prevent future exacerbations in a substantial proportion of COPD patients (3). A high blood eosinophil count may be a biomarker to identify these patients and may be a useful to determine the most appropriate treatment for people with COPD. Blood eosinophils may help to identify patients who may benefit from ICS treatment (4) and who are at risk of exacerbations if ICS are withdrawn (5) and to direct treatment for exacerbations (6).
COPD prescription costs are high and rising and often inappropriate (2). Thus, there is a need for understanding who are high resource patients and how to identify them.

To our knowledge there is no information available on the burden and cost of COPD in patients with high blood eosinophil counts who are at risk of exacerbations despite receiving treatment with triple therapy.

This study aims to evaluate the role of high blood eosinophil counts measured during stable disease in the burden and costs of COPD in a broad real-life population of patients in the UK.

**Objectives:**

Observational historical follow-up studies investigating the role of blood eosinophils in the burden and costs of COPD with the following objectives:

1. To study the association between high blood eosinophil counts at the time of stable COPD (i.e., no recent exacerbation and stable treatment during the study period) and the prospective exacerbation rate in different subgroups of patients with COPD defined by treatment regimen and smoking habits and to study whether this association is also found in patients with good adherence to ICS

2. To study whether patients admitted to hospital for COPD exacerbation are more likely to be re-admitted if their pre-admission eosinophil count (assessed at the time when there was no recent exacerbation) is high

3. A. To estimate mean all-cause and COPD-related health care resource use (HRU) and associated costs in 4 subgroups of patients who are at risk of exacerbations (i.e. a history of ≥2 exacerbations or ≥1 exacerbation leading to hospitalisation in the past 12 months) while receiving treatment with triple therapy, where the 4 subgroups are defined by the presence or absence of high blood eosinophil counts and current smoking habits
   B. to compare HRU and costs with those for the total population of patients with COPD who have blood eosinophil counts available

4. To study whether the presence of high blood eosinophil counts is associated with greater all-cause and COPD-related costs in the subsequent year and to study which other easily accessible characteristics drive future costs in patients with COPD

**Methods:**

**Study design:**

An observational historical cohort study will be performed among the UK population of patients with COPD who have blood eosinophil counts available.
Patients will be characterised in a baseline year prior to the index date (ID) and outcomes will be measured in the year after ID.

**Data Sources:**

Analyses for sub-study 1 (association between high eosinophil counts and COPD exacerbations) will be performed in patients from OPCRD. A subpopulation of patients from CPRD with linkage to Hospital Episode Statistics (HES) available will be selected for sub-studies 2−4 (association between high blood eosinophil counts and the risk of hospital re-admission for COPD and study on HRU and costs)

**Study Population:**

The index date (ID) will be the most recent blood eosinophil count measurement, except for sub-study 2 for which the hospital discharge date of the most recent first hospitalization for COPD within one year after a blood eosinophil count measurement will be used as ID. Eligible patients should be ≥40 years old and have at least 1 year of continuous data prior to and after the respective IDs, except for sub-study 2 in which patients who die or who are lost to follow-up in the outcome year are censored. Patients eligible for sub-study 1 need to be on stable treatment during the study period.

**Exposures:**

Only eosinophil counts measured when there was no recent (4 weeks) exacerbation recorded are considered. The primary definition of high blood eosinophil counts will be $\geq 0.45 \times 10^9$/L, based on previous work. Sensitivity analyses will be performed using $\geq 0.25$, $\geq 0.35$ and $\geq 0.55 \times 10^9$/L as the definition.

**Outcomes:**

The primary outcome measure for objective 1 will be the number of COPD exacerbations during the outcome year. The number of oral steroids courses will be analysed as secondary outcome.
The occurrence of a re-admission to hospital with COPD exacerbation at any diagnostic position within 4 weeks, 12 weeks and 1 year after discharge from hospital will be the primary outcome measure for objective 2.
HRU and costs will be outcomes for objectives 3 and 4.

**Sample Size Estimations:**

For objective 1, a total of 1,645 patients are required for each therapy group to find a significant ($\alpha$=0.05) Rate Ratio of 1.3 as previously found with 80% power, when analysing the association between high blood eosinophil counts and the number of exacerbations, assuming 10% of patients having high blood eosinophil counts and a mean rate of events of 0.68 in patients without high blood eosinophil as found in a previous study conducted by OPRI.

For objective 2, around 10,000 patients hospitalized for COPD with a blood eosinophil count available within one year prior to ID are required for finding a hazard ratio of 1.3 for the association between a high blood eosinophil count and re-admission risk, assuming a re-admission risk of 10% within 4 weeks in patients with normal eosinophil counts.

For objective 3, a total number of 980 patients with ≥2 exacerbations in the baseline year while receiving triple therapy are required to find a 0.3 standard deviation greater

amount of (the logarithm) of total costs in patients with high blood eosinophil counts compared with patients with normal counts.

For objective 4, a total number of 2,200 patients are required for finding a significant difference of 0.2 standard deviations between the means of (the logarithm) of total costs of patient groups with and without high blood eosinophil counts.

**Statistical Analysis:**

Negative binomial regression will be performed to estimate Rate Ratios with 95% confidence intervals (CI) for the association between high blood eosinophil counts and the number of COPD exacerbations in the outcome year, stratified by different treatment options and current smoking habits, adjusted for potential confounders assessed at baseline.

Analyses will be performed in patients on different treatment regimens, adjusted for potential confounders (see paragraph 3.3.2 ) in two populations:

1. The full population of patients with COPD
2. A subpopulation of patients with "classical COPD" who had $FEV_1/FVC < 0.70$ recorded within 5 years prior to the index date, never received an asthma diagnosis and have a smoking history

Whether the association is modified by the Medication Possession Ratio (MPR) for ICS in the baseline year will be studied by including an interaction term of eosinophil count and MPR into the regression model and by repeating the analyses in patients adherent to treatment (MPR≥80%).

Risks of re-admission to hospital for COPD will be reported in a life-table and Kaplan-Meier curves will be constructed for patients with and without high eosinophil counts within 4 and 12 weeks and 1 year after hospital discharge. Comparisons will be made with the use of a log-rank analysis. Cox-proportional hazard regression with the time from hospital discharge date to the first re-admission date as time to event will be performed to estimate Hazard Ratios with 95% CI for the association between high eosinophil counts and time to re-admission, adjusted for potential confounders.

HRU and costs will be described in the baseline and outcome years. Mean costs with standard deviations will be estimated for subgroups of patients based on reference costs published by the UK National Health Service (NHS). Cost ratios with 95% CI will be estimated for comparison of costs with the overall mean in the total population of patients with COPD.

A one- or two-step generalized linear model with gamma distribution and log link will be used to perform regression analysis with total costs as the outcome variable.
All candidate predictors will be fed into a multiple regression analysis with backwards selection of the model with the best fit based on Akaike's information criterion (AIC).

An interaction term of blood eosinophil counts and smoking status will be included in the model as potential predictor next to the main effects to evaluate relevant modification of the independent effect of blood eosinophil counts by different smoking habits. Relative costs will be estimated from the model for patients with and without high blood eosinophil counts.

# AMENDMENT HISTORY

| Date | Brief description of change | Administrative Change / Amendment / New Protocol Version. |
|---|---|---|
| 11 October 2016 | First draft protocol for AZ review | V1.0 |
| 31 October 2016 | Revised draft protocol after AZ review | V2.0 |
| 18 November 2016 | Revision following comments SC | V3.0 |

# MILESTONES

| Date | Milestone |
|---|---|
| 11 November 2016 | Final protocol and statistical analysis plan |
| 16 December 2016 | Delivery report sub-study 1: association between high blood eosinophil counts and COPD exacerbations rates |
| 23 December 2016 | Delivery report sub-study 2: association between high blood eosinophil counts and hospital re-admission rates |
| 23 January 2017 | Delivery report sub-study 3: HRU and costs in subgroups of COPD patients |
| 6 March 2017 | Manuscript submission sub-studies 1 & 2 |
| 16 March 2017 | Delivery report sub-study 4: patient's characteristics that drive future all-cause and COPD-related costs |
| 6 July 2017 | Manuscript submission sub-studies 3 & 4 |

# 1. BACKGROUND AND RATIONALE

## 1.1 Background

In the UK, 4.5% of all people aged over 40 are estimated to live with diagnosed Chronic Obstructive Pulmonary Disease (COPD), based on Read codes recorded in Electronic Medical Records (7). The UK is among the top 20 countries for COPD mortality worldwide (8).

COPD is a heterogeneous condition with patients showing varying clinical and pathophysiological features. The identification of COPD phenotypes with distinct characteristics may allow targeted treatment strategies directed towards specific biological pathways.

Eosinophilic inflammation is thought to be a characteristic feature of asthma rather than COPD. However, studies have shown that there is a subset of COPD patients with eosinophilic airway inflammation, even after exclusion of patients with any features of asthma (1). Interestingly, this subset of patients with COPD exhibit the greatest response to corticosteroid treatment (4, 9) and tailoring of therapy based on sputum eosinophil counts is more effective in reducing exacerbations than treatment according to traditional guidelines (5). This suggests that there is a sub-phenotype of COPD with an eosinophilic type of airway inflammation similar to that observed in patients with asthma (10).

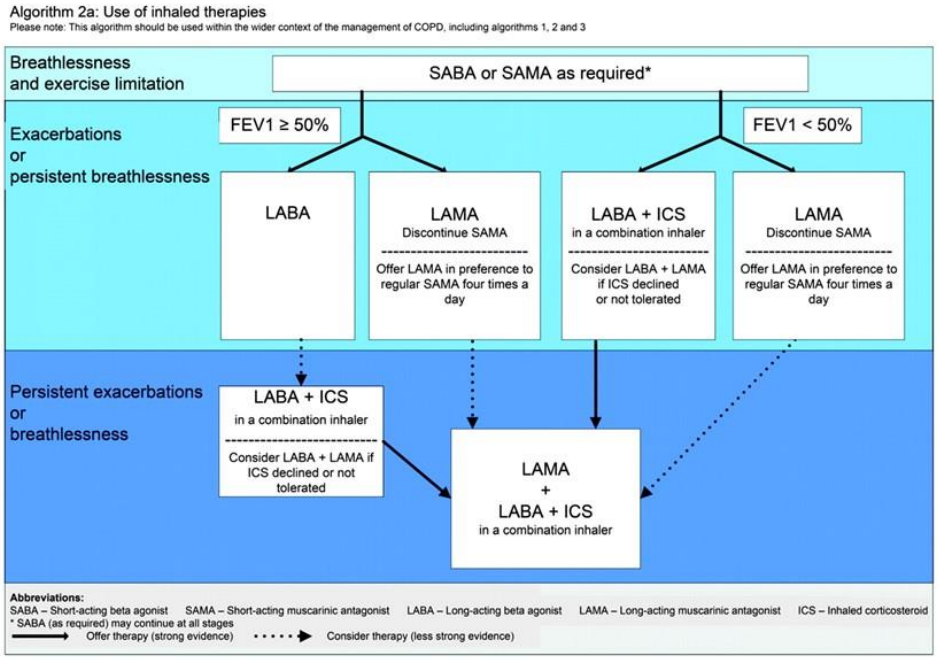
In a study performed in patients with COPD from the general population of Denmark, blood eosinophil levels above $0.34 \times 10^9$ /L were associated with a 1.76-fold increased risk for severe COPD exacerbations requiring hospitalization and with a 1.15-fold increased risk for exacerbations not requiring hospital admission (11).
Previous work conducted at OPRI confirmed the increased risk of exacerbations with high blood eosinophil counts in real-life UK patients with COPD from the Optimum Patient Care Research Database (OPCRD) when using a higher cut-point of $\geq 0.45 \times 10^9$ / L, observed in 10% of the population (submitted for publication). However, the association was limited to patients who were not actively smoking. Ex-smokers with high blood eosinophil counts showed a 32% higher rate of exacerbations than ex-smokers with normal eosinophil counts. The association was found in patients treated with ICS and in patients in GOLD groups B to D, and was not influenced by any prior recording of asthma.

To date, guidelines mention that no treatment has been shown to influence the accelerated decline in lung function that is characteristic of COPD, highlighting the limited treatment options for this patient population (12). Post-hoc analyses of trial data suggest that patients with high blood eosinophil counts may benefit from inhaled corticosteroids (ICS) treatment in terms of a lower rate of decline in $FEV_1$ (13), but this requires confirmation in specifically designed studies. Both NICE and GOLD strategy documents recommend the use of ICS as part of a fixed dose combination (FDC) ICS/LABA treatment for patients who have 2 or more exacerbations per year or moderate to severe airflow limitation ($FEV_1$ <50% predicted normal) (GOLD groups C and D) (Figure 1). Most ICS/LABA combinations are indicated for symptomatic treatment of patients with COPD with $FEV_1 \leq 70\%$ predicted.
However, there is an increasing body of evidence suggesting a link between treatment with

high doses of ICS and the risk of comorbidities, such as cataracts, osteoporosis and pneumonia events, clearly associated with systemic/oral corticosteroids (14-17).

Despite these guidelines, real-world studies indicate that pharmacological treatments often differ from the recommendations. ICS is frequently prescribed to patients with less severe COPD (2). This may reflect the heterogeneity of COPD with different treatment effects of ICS in different subgroups of patients with COPD.

**Algorithm showing use of inhaled therapies.**




**John O'Reilly, and Michael Rudolf Thorax 2011;66:93-96**

THORAX



**Figure 1. COPD Therapy guidelines by NICE (16).**

COPD is associated with high mortality and morbidity. Hospitalizations for acute exacerbations of COPD account for a relatively large proportion of annual direct costs for COPD (3). Furthermore, one in five patients is estimated to require re-hospitalization within 30 days of discharge after an admission for acute exacerbation, indicating a lack of effectiveness of standard treatment to prevent future exacerbations in a substantial proportion of COPD patients (3). A recent study found that patients with relatively low blood eosinophil counts (≤2%) and high CRP levels measured at exacerbation had higher re-admission rates during 6 months of follow up than eosinophilic patients (18). However, low blood eosinophil

counts during exacerbations are a marker of bacterial infection (19), which does not exclude high blood eosinophil counts at the time of stable disease to be a risk factor of COPD re-admission after therapy failure.
There is sparse evidence available that high blood eosinophil counts present at the time of stable disease are associated with increased all-cause mortality during long-term follow-up (20).

This study aims to evaluate the role of high blood eosinophil counts measured during stable disease in the burden and costs of COPD in a broad real-life population of patients in the UK.

## 1.2 Rationale

Previous work conducted at OPRI found an increased risk of exacerbations with high blood eosinophil counts. However, the role of different treatment regimens in the association between blood eosinophil count and COPD exacerbations needs to be further elucidated. It is unknown whether the association is also present in the subgroup of patients with COPD who are adherent to ICS and in patients on triple therapy, to which one third of UK patients with COPD progresses in real life (2).

It is also unknown whether patients who have high blood eosinophil counts at the time of stable disease and who experience an exacerbation that requires hospitalization have an increased risk of short-term recurrence of exacerbations and re-admission to hospital.

To our knowledge there is no information available on the burden and cost of COPD in patients on triple therapy who have high blood eosinophil counts and experience frequent exacerbations.

## 1.3 Hypotheses

A high blood eosinophil count present at the time of no exacerbation is a biomarker identifying a phenotype of COPD associated with an increased rate of exacerbations at all levels of treatment in patients who are not actively smoking. High blood eosinophil counts are associated with an increased risk of short-term re-admission to hospital for COPD exacerbation.

Medical costs associated with COPD are meaningfully higher in patients with high blood eosinophil counts than in patients with normal counts.
Especially the subgroup of patients with COPD on triple therapy who have high blood eosinophil counts and are at risk of exacerbation account for high future health care resource use (HRU) and associated costs.

## 1.4 Objectives

1. To study the association between high blood eosinophil counts at the time of stable COPD (i.e., no recent exacerbation and stable treatment during the study period) and the prospective exacerbation rate in different subgroups of patients with COPD defined by treatment regimen and smoking habits and to study whether this association is also found in patients with good adherence to ICS

2. To study whether patients admitted to hospital for COPD exacerbation are more likely to be re-admitted if their pre-admission eosinophil count (assessed at the time when there was no recent exacerbation) is high

3. A. To estimate mean all-cause and COPD-related health care resource use (HRU) and associated costs in 4 subgroups of patients who are at risk of exacerbations (i.e. a history of ≥2 exacerbations or ≥1 exacerbation leading to hospitalisation in the past 12 months) while receiving treatment with triple therapy, where the 4 subgroups are defined by the presence or absence of high blood eosinophil counts and current smoking habits
   B. to compare HRU and costs with those for the total population of patients with COPD who have blood eosinophil counts available

4. To study whether the presence of high blood eosinophil counts is associated with greater all-cause and COPD-related costs in the subsequent year and to study which other easily accessible characteristics drive future costs in patients with COPD

# 2. METHODOLOGY

## 2.1 Study Design – General Aspects

### 2.1.1 Data Sources

Dataset of patients from Clinical Practice Research Datalink (CPRD) and the Optimum Patient Care Research Database (OPCRD) will be used for analyses.

CPRD[1], formerly known as the General Practice Research Database (GPRD), is a computerised longitudinal research database containing anonymised medical record data from approximately 650 subscribing UK primary care practices.

OPCRD[2] is a respiratory-enriched primary care research database compiled by Optimum Patient Care providing chronic respiratory review services. It contains anonymous, longitudinal data extracted from over 550 UK practices (>178.000 patients with COPD). It is approved by Trent Multi Centre Research Ethics Committee for clinical research use and offers a high-quality data source that is used regularly in clinical, epidemiological and pharmaceutical research.

Both datasets are constructed separately using data in a patient unidentifiable manner

Sub-study 1 will use patient data extracted from the Optimum Patient Care Research Database (OPCRD). The OPCRD is developed, maintained, and owned by Optimum Patient Care (OPC), 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.

For sub-studies 2, 3 and 4, data of patients from the Clinical Practice Research Datalink (CPRD) with linkage to HES Admitted Patient Care and HES A&E and outpatient datasets will be used. CPRD data will be extracted through AZ's account.

[1] https://www.cprd.com
[2] See http://optimumpatientcare.org/opcrd/

## 2.2 Study Population

The study population consists of patients with diagnosed COPD who are registered at general practices providing data to OPCRD and who have at least one blood eosinophil count available. For objectives 2, 3 and 4 patients from CPRD who have linkage to HES will be selected.

## 2.3 Inclusion Criteria

*Overall inclusion criteria:*

1. A diagnostic Read code for COPD[3] qualifying for inclusion in the register of patients with COPD recorded after 1st April 2008 (21)
2. Age ≥ 40 years at the most recent diagnostic code and at index dates
3. ≥ 1 valid blood eosinophil count measured when there was no recent exacerbation recorded, i.e., within 4 weeks prior to or at the measurement
4. Valid continuous data in a baseline year prior to index date
5. At least one year of continuous outcome data after the index date, except for patients included in the study of objective 2, in which patients lost to follow up are censored

*Objective-specific inclusion criteria:*

6. Objective 1:
   Stable COPD therapy, i.e. no change in treatment regimen, ICS dosage and substance during baseline and outcome years

7. Objective 2:
   a. Hospital discharge of admission with COPD exacerbation as diagnosis
   b. Blood eosinophil count measured at the time of no recent exacerbation within 1 year prior to ID

8. Objectives 2, 3 and 4:
   Linkage to HES data available

## 2.4 Exclusion Criteria

1. Diagnostic Read code for the following chronic lower respiratory conditions ever:
   a. Pulmonary sarcoidosis
   b. Hypersensitivity pneumonitis
   c. Malignancy of the lungs
   d. Interstitial Lung Disease
   e. Cystic fibrosis
2. Chronic treatment with oral corticosteroids

[3] In the UK, a diagnosis of COPD under the terms of the Quality Outcome Framework of the GP General Medical Services Contract requires a diagnostic procedure for COPD following NICE guidelines[2]. This includes the requirement that airflow obstruction is confirmed by post-bronchodilator spirometry as from 1st April 2008. http://www.hscic.gov.uk/qof

(Patients with a concurrent diagnosis of asthma will be included)

## 2.5 Study designs

### 2.5.1 Objective 1

The index date (ID) of objective 1 will be the most recent date of a recorded blood eosinophil count, measured at the time of stable disease, defined as no COPD exacerbation within 4 weeks prior to or at ID and no change in treatment regimen, ICS dosage and substance during the study period (Figure 1).

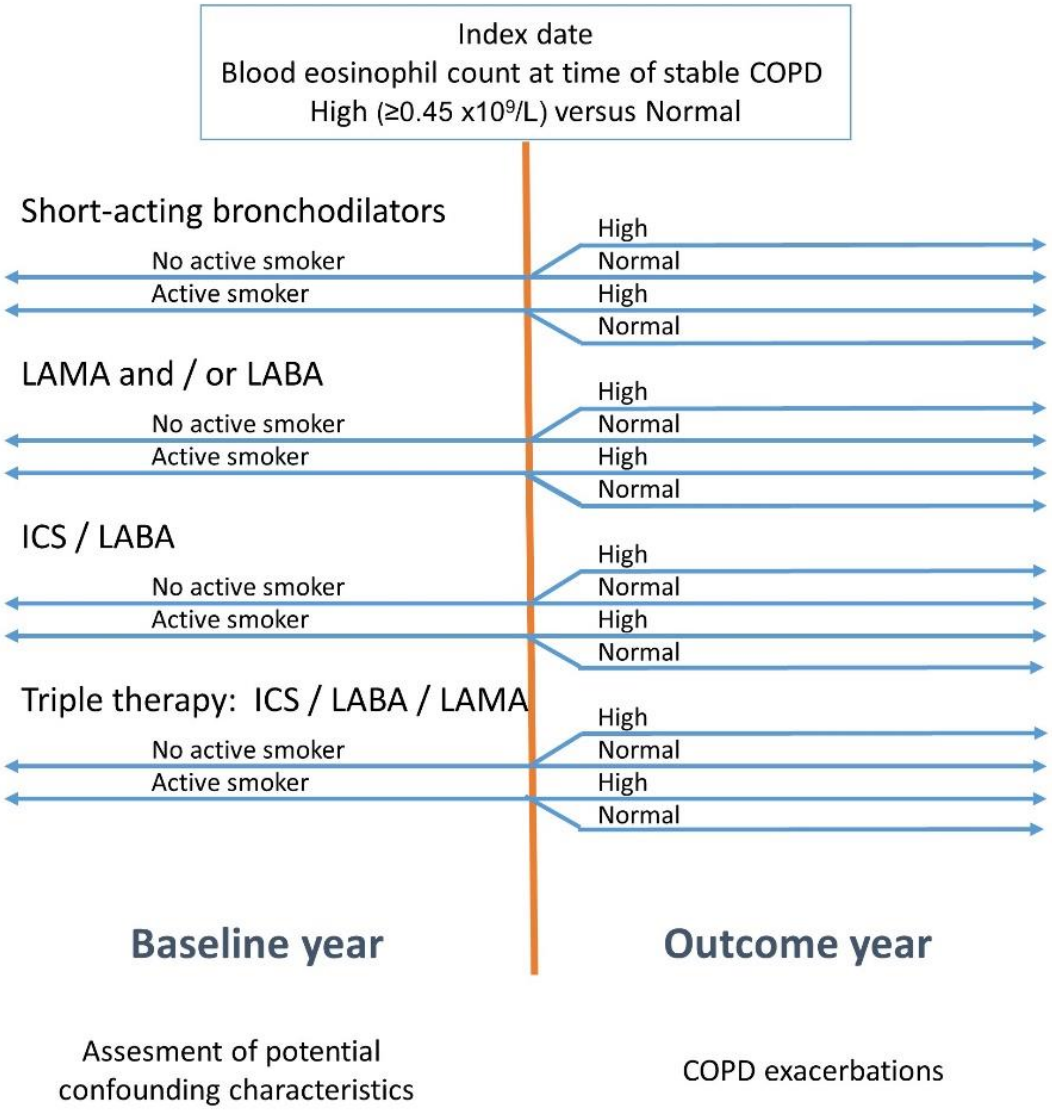



**Figure 2. Study design objective 1**

Patient's demographics and clinical characteristics will be described and potential confounders will be assessed in a baseline year prior to ID.
The association between high blood eosinophil counts (at ID) and (moderate or severe) COPD exacerbations in the subsequent year will be assessed in subgroups of patients defined by smoking status (active smoker in baseline year or not) and the following treatments in the baseline year (22):

1. Short-acting bronchodilators as required only (SABA and/or SAMA)
2. Maintenance therapy with LAMA and/or LABA
3. ICS / LABA in combination inhaler
4. Triple therapy: ICS + LABA + LAMA

The primary definition of "high eosinophil counts" will be ≥0.45 x $10^9$/L, based on our previous work. Sensitivity analyses will be performed using 0.25, 0.35 and 0.55 as cut-points.

Sensitivity analyses will be performed in the subgroup of patients with COPD who have never been diagnosed with asthma, i.e., no diagnostic Read code for asthma recorded ever.

Additional analyses will be performed to evaluate whether the Medication Possession Ratio (MPR) for maintenance treatments (ICS / LAMA / LABA) modifies the associations by:

1. Including interaction terms of blood eosinophil counts and MPR into the regression model (continuous or categorical depending on best model fit) to explore whether MPR significantly modifies the association and at which values
2. Repeating analyses in patients with good adherence to ICS, using the widely used cut-point of MPR≥80% for therapy options 3 and 4

### 2.5.2 Objective 2

The ID of objective 2 will be the date of the most recent first discharge from hospital admission for COPD exacerbation occurring within one year after a blood eosinophil count measured at the time of no recent exacerbation (Figure 3). Patients will be followed after ID until re-admission or death to a maximum of one year after each index date.

The risk of COPD-related re-admission to hospital for COPD within 4 weeks and 1 year will be compared for patients with and without high blood eosinophil counts year prior to index date. All analyses will be adjusted for potential confounders in multiple regression analysis.

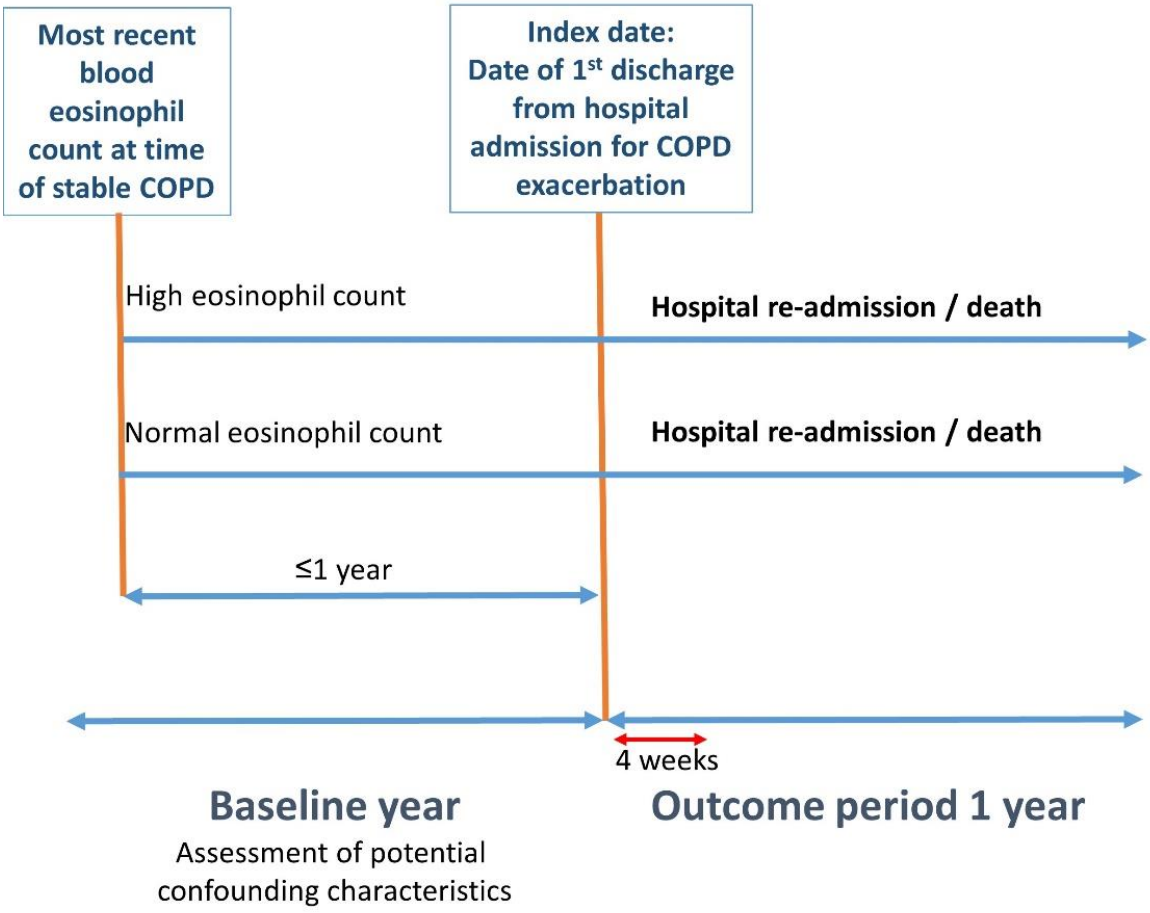



**Figure 3. Study design objective 2**

### 2.5.3 Objective 3

The ID of objective 3 will be the most recent blood eosinophil count recorded at the time of no recent exacerbation (Figure 4).
HRU and costs, broken down by type of utilisation and total costs will be assessed in both a baseline year prior to ID and a follow-up year (outcome year) after ID.

Mean all-cause and COPD-related HRU and associated costs will be estimated in one follow-up year after the eosinophil count in the following 4 subpopulations, defined in a baseline year, of patients with COPD on triple therapy, who are at high risk of exacerbations (i.e. a history of ≥2 exacerbations or ≥1 exacerbation leading to hospitalisation in the baseline year):

Patients with high blood eosinophil counts who are:
1. not actively smoking
2. actively smoking

Patients with normal blood eosinophil counts who are:
3. not actively smoking
4. actively smoking

Mean HRU and costs will be compared with values observed in the total population of patients with COPD who have blood eosinophil counts available.

**Figure 4. Study design 2**

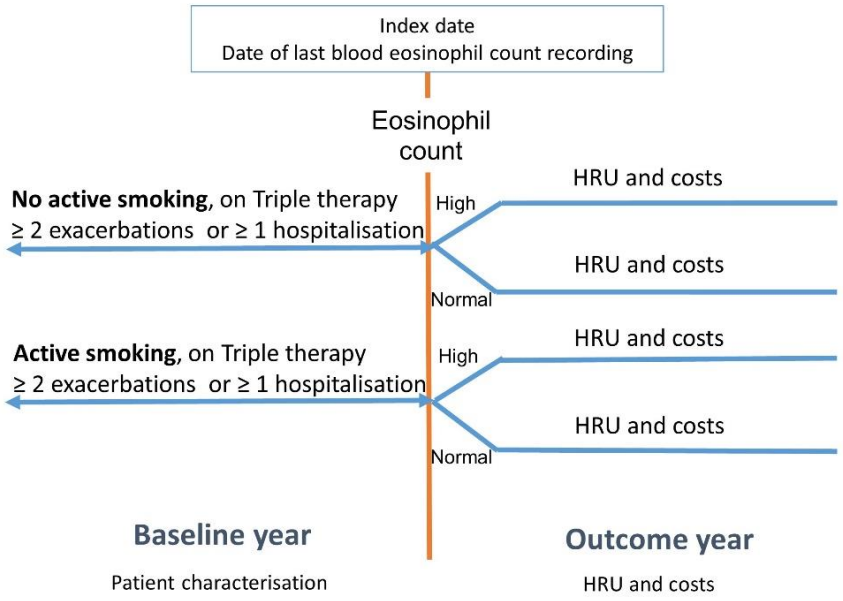



**Figure 4. Study design objective 3**

### 2.5.4 Objective 4

The ID of objective 4 will be the most recent blood eosinophil count recorded at the time of no recent exacerbation with one baseline year prior to index date for assessment of potential predictors of costs.
Total all-cause and COPD-related medical costs will be assessed in the outcome year after ID (Figure 5).

Two multiple regression analyses will be performed with total all-cause costs and total COPD-related costs as outcome variables. All potential predictors will be evaluated as independent variables, including blood eosinophil counts and its interaction with smoking status.

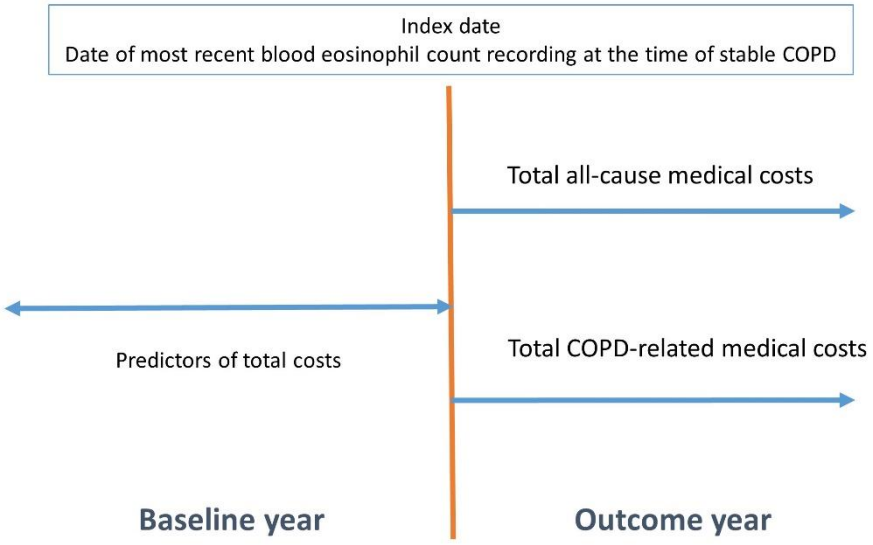



**Figure 5. Study design objective 4**

# 3. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

## 3.1 Determinants of COPD exacerbations

### 3.1.1 Definition of high blood eosinophil counts

Only eosinophil counts measured at the time of stable COPD will be eligible for selection at the most recent measurement. Stable COPD is defined as absence of a recorded COPD exacerbation within 4 weeks prior to or at the eosinophil count recording date, as our previous work showed that eosinophil counts were relevantly decreased within patients when oral corticosteroids courses were prescribed within 4 weeks prior to ID and when antibiotics were prescribed at ID.

The primary definition of high blood eosinophil counts will be $\geq 0.45 \times 10^9$/L, based on previous work. Sensitivity analyses will be performed using $\geq 0.25$, $\geq 0.35 \times 10^9$/L and $\geq 0.55 \times 10^9$/L as cut-points.

A sensitivity analysis adjusted for the neutrophil count / neutrophil-to-lymphocyte ratio as markers of infection (23) will be performed in patients who have these measurements available.

### 3.1.2 Treatment regimens

For objective 1, groups of patients using the following treatment regimens are analysed:

1. Short-acting bronchodilators as required only (SABA and/or SAMA)
2. Maintenance therapy with LAMA and/or LABA
3. ICS / LABA in combination inhaler
4. Triple therapy: ICS + LABA + LAMA

Treatment category will be assessed based on ≥1 prescriptions in the baseline year.

### 3.1.3 Medication Possession Ratio

MPR (the proportion of days covered by prescriptions) will be calculated by dividing the total of one day's supply by the total number of days evaluated, multiplied by 100%. The evaluation period for every person is 365 days in the baseline year.

## 3.2 Outcomes

### 3.2.1 COPD exacerbations

The primary outcome for sub-study 1 will be the number of COPD exacerbations in the outcome period, defined as the occurrence of one or more of the following events:

a. Respiratory-related hospital attendance / admission AND/OR
b. Respiratory-related A&E attendance AND/OR
c. An acute oral corticosteroid course AND/OR
d. Antibiotics prescribed with evidence of a lower respiratory consultation

Where ≥1 of these events occur within 2 weeks of each other, they will be considered to be the result of the same exacerbation (and will only be counted once).

The number of acute oral corticosteroids courses will be analysed as secondary outcome for sub-study 1.

A sensitivity analysis will be performed with a more specific (but less sensitive definition) of acute oral corticosteroids courses with evidence of a lower respiratory consultation (Read code for lower respiratory consultation with prescription).

### 3.2.2 Hospital admissions in HES linked data

1. Hospital admissions as the index date for objective 2:
   Occurrence of a hospital admission (spell) for COPD exacerbation in HES linked data:
   ≥1 of the following ICD-10-CM codes in any diagnostic position (Appendix 6.1):
   a. J44.0: Chronic obstructive pulmonary disease with acute lower respiratory infection
   b. J44.1: Chronic obstructive pulmonary disease with (acute) exacerbation
2. Hospital re-admission as outcome event:
   Occurrence of a hospital admission (spell) for COPD in HES linked data:
   a. ICD-10 codes J44.0 or J44.1: COPD exacerbations in any diagnostic position
   b. ICD-10 codes J40-J44: any COPD-related code as primary diagnosis

### 3.2.3 Mortality

1. All-cause mortality will be assessed by the combined information on:
   a. Death in hospital, based on HES data
   b. Death outside hospital, based on GP records

### 3.2.4 Health care Resource Use

The following outcomes of HRU are described in the baseline year and outcome year in patients with HES data available.[4]

1. Physician office visits:
    a. Total number of General Practice (GP) surgery consultations
    b. Number of COPD-related GP consultations
2. Outpatient visits:
    a. Total number of referrals to specialist
    b. Number of referrals to specialist for COPD or other lower respiratory conditions
3. Accident & Emergency (A&E) attendances / out of hours services:
    a. Total number of A&E attendances
    b. Total number of GP out-of-hours consultations
    c. Number of A&E attendances for COPD or other lower respiratory conditions
4. Hospital admissions: Number of hospital admissions (spells):
    a. For all-causes
    b. With COPD exacerbations (ICD-10 J44.0 or J44.1) as primary diagnosis
    c. With COPD exacerbations ICD-10 J44.0 or J44.1) as secondary / subsidiary diagnosis and respiratory conditions (ICD-10 J00-J99) as primary diagnosis
5. Number of COPD-related drug prescriptions:
    a. Fixed dose combination (FDC) of inhaled corticosteroids (ICS) and Long-acting β2-agonists (LABA)
    b. Stand-alone ICS
    c. Stand-alone LABA
    d. Stand-alone LAMA
    e. FDC LAMA / LABA
    f. Short-acting β2-agonists (SABA)
    g. Short-acting Muscarinic Antagonists (SAMA)
    h. Theophylline
    i. Oral corticosteroids
    j. Antibiotics prescribed with lower respiratory consultation Read code
6. Total number of drug prescriptions for all causes

Outcomes are described as mean numbers (± standard deviation (SD)) and as categorical variables (0, 1, 2, 3, ≥4 for outpatient visits, A&E attendances and hospitalisations; 0, 1-4, 5-8, 9-12, 13-24, ≥25 for GP consultation; ≥1 prescription (yes/no) for drugs)

[4] Events occurring at index date are counted in the baseline year, except medication prescriptions which are counted in the outcome year

### 3.2.5 Costs of Health care Resource Use

Cost data for primary consultation services provided are obtained from the most recent publication of the 'Unit Costs of Health & Social Care', prepared by the Personal Social Services Research Unit (PSSRU) at the time of analyses.

Costs for COPD or respiratory related services provided in secondary care are obtained from 'NHS Reference cost schedule 2014 to 2015', prepared by the Department of Health[5] or a more recent version when available.

Prices assigned to drugs are taken from the NHS dictionary of medicines and devices (DM+D) browser (http://dmd.medicines.org.uk/). DM+D provides up to date costs for Systematized Nomenclature of Medicine Clinical Terms (SnoMed) codes. Read codes are mapped to SnoMed codes and costs are calculated for the following medications:

1. Inhaled Corticosteroids (ICS)
2. Long-Acting ß-2 Agonists (LABA)
3. Short-Acting ß-2 Agonists (SABA)
4. Short-Acting Muscarinic Antagonists (SAMA)
5. Long-Acting Muscarinic Antagonists (LAMA)
6. Oral corticosteroids (maintenance and rescue courses)
7. Theophyllines
8. Antibiotics prescribed for lower respiratory events

Total all-cause and COPD-related costs are calculated as the sum of costs related to the respective HRU outcomes mentioned above.

[5] https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015

## 3.3 Other Variables and Covariates

### 3.3.1 Patient demographics / baseline characterisation

The following baseline characteristics will be described for comparison groups:

1. Age group at index date (years):
2. Sex
3. Smoking status, Read code closest to and within 5 years prior to index date
    a. Never smoker
    b. Ex-smoker
    c. Current smoker
4. BMI, calculated from height and weight data if available[6] and taken from practice recorded BMI value if not, within 10 years prior to index date
    a. Underweight: <18.5
    b. Normal weight: ≥18.5 and <25
    c. Overweight: ≥25 and <30
    d. Obese: ≥30
5. Comorbidities (Diagnostic Read code prior to index date):
    a. Asthma
        a. Never
        b. Active[7]
        c. Ever, not active
    b. Allergic / non-allergic rhinitis
        a. Never
        b. Active
        c. Ever, not active
    c. Eczema diagnosis
        a. Never
        b. Active
        c. Ever, not active
    d. Nasal polyps ever
    e. Helminth infections
    f. Chronic sinusitis diagnosis ever
    g. Gastro-oesophageal reflux disease (GERD)
    h. Diabetes Mellitus ever
    i. Osteopenia / Osteoporosis ever
    j. Hypertension ever
    k. Obstructive Sleep apnoea ever
    l. Cataract ever
    m. Ischaemic heart disease ever
    n. Heart failure ever

[6] Weight (kg) divided by height (metres) squared
[7] For comorbidities, 'active' refers to those for which a diagnosis was recorded within the baseline year and/or a prior diagnosis was accompanied by a prescription for the comorbidity within the baseline year. 'Ever' refers to diagnosis at any time before or during the baseline period

o. Psychiatric conditions / Anxiety/ Depression ever
p. Sleep disorders ever
q. Chronic kidney disease ever
r. Osteoporosis (Read code diagnosis or osteoporosis drugs [bisphosphonates, denosumab, strontium ranelate or teriparatide] ever

6. Charlson co-morbidity index: based on diagnoses ever
    a. 0
    b. 1-4
    c. 5-9
    d. ≥10
7. Most recent $FEV_1$ % predicted, mean (SD) and categorical
    a. ≥80%
    b. 50–79%
    c. 30-49%
    d. <30%
    e. Unknown
8. Modified Medical Research Council (MRC) dyspnoea score, within 5 years of the index date
    a. 0-1
    b. ≥2
    c. Unknown
9. GOLD groups, defined based on a combined assessment of symptoms, spirometry and exacerbation risk as follows:
    a. GOLD A: $FEV_1$ % predicted ≥50 and ≤1 COPD exacerbation and no hospitalization for COPD in baseline year and mMRC 0–1
    b. GOLD B: $FEV_1$ % predicted ≥50 and ≤1 COPD exacerbation and no hospitalization for COPD in baseline year and mMRC ≥2
    c. GOLD C: $FEV_1$ % predicted <50 or ≥2 COPD exacerbations or ≥1 hospitalization for COPD in baseline year) and mMRC 0–1
    d. GOLD D: $FEV_1$ % predicted <50 or ≥2 COPD exacerbations or ≥1 hospitalization for COPD in baseline year) and mMRC ≥2
    e. Unknown
10. ICS/LABA combinations prescribed with dosages (most recent in the baseline year)
    a. Budenoside / formeterol (Symbicort® / DuoResp Spiromax®)
    b. Fluticasone propionate / salmeterol (Seretide®)
    c. Beclomethasone / formeterol (Fostair®)
    d. Fluticasone furoate / vilanterol (Relvar Ellipta®)
11. Cumulative doses prescribed in the baseline year (expressed as average dose per day):
        a. Average cumulative ICS dose
        b. Average cumulative SABA dose
        c. Average cumulative SAMA dose

### 3.3.2 Potential confounders of association between high eosinophil counts and outcomes

Analyses will be adjusted for the following potential confounders:

1. Age
2. Sex
3. Smoking status
4. BMI
5. Asthma
    a. Never
    b. Active[8]
    c. Ever, not active
6. Allergic / non-allergic rhinitis:
    a. Never
    b. Active
    c. Ever, not active
7. Eczema diagnosis:
    a. Never
    b. Active
    c. Ever, not active
8. Nasal polyps ever
9. Charlson comorbidity index

### 3.3.3 Candidate predictors of total costs

1. Age
2. Sex
3. Smoking status
4. BMI
5. Blood eosinophil count
6. Most recent MRC score
7. Most recent $FEV_1$ % predicted, with separate category for missing
8. Baseline number of exacerbations
9. Comorbidities (Diagnostic Read code prior to index date):
    a. Asthma ever
    b. Allergic / non-allergic rhinitis
        a. Never
        b. Active[9]
        c. Ever, not active
    c. Eczema diagnosis

[8] For comorbidities, 'active' refers to those for which a diagnosis was recorded within the baseline year and/or a prior diagnosis was accompanied by a prescription for the comorbidity within the baseline year. 'Ever' refers to diagnosis at any time before or during the baseline period

[9] For comorbidities, 'active' refers to those for which a diagnosis was recorded within the baseline year and/or a prior diagnosis was accompanied by a prescription for the comorbidity within the baseline year. 'Ever' refers to diagnosis at any time before or during the baseline period

    a. Never
    b. Active
    c. Ever, not active
  d. Nasal polyps ever
  e. Chronic sinusitis diagnosis ever
  f. Gastro-oesophageal reflux disease (GERD) ever
  g. Diabetes Mellitus ever
  h. Osteopenia / Osteoporosis ever
  i. Hypertension ever
  j. Obstructive Sleep apnoea ever
  k. Cataract ever
  l. Ischaemic heart disease ever
  m. Heart failure ever
  n. Psychiatric conditions / Anxiety/ Depression ever
  o. Sleep disorders ever
  p. Chronic kidney disease ever
  q. Osteoporosis (Read code diagnosis or osteoporosis drugs [bisphosphonates, denosumab, strontium ranelate or teriparatide] ever
10. Charlson comorbidity index
11. Therapy prescribed in the baseline year (yes/no)
    a. ICS / LABA
    b. SABA
    c. SAMA
    d. LAMA
    e. Theophylline

## 3.4 Statistical Methods – General Aspects

Summary statistics are provided for all baseline and outcome variables, for the complete dataset and by comparison groups. For continuous variables, these include:

- Sample size (n)
- Percentage non-missing
- Mean ± Standard Deviation for normally distributed variables
- Median and Inter-quartile Range ($25^{th}$ and $75^{th}$ percentiles) for non-normally distributed variables

For number of events per year, the summary statistics include:

- Sample size (n)
- Count and Percentage by category (distribution): 0, 1, 2, 3 and ≥4

For other categorical variables, the summary statistics include:

- Sample size (n)
- Count and Percentage by category (distribution)

Characteristics are compared using the chi-squared test for categorical variables and a Student's t-test for normally distributed continuous variables or a Mann-Whitney test for non-normally distributed continuous variables.

### 3.4.1 Outcome analyses sub-study 1

Analyses will be performed in patients on different treatment regimens, adjusted for potential confounders (see paragraph 3.3.2) in two populations:

1. The full population of patients with COPD
2. A subpopulation of patients with "classical COPD" who had $FEV_1/FVC < 0.70$ recorded within 5 years prior to the index date, never received an asthma diagnosis and have a smoking history

Negative binomial regression is performed to estimate RRs with 95% CI for the association between high blood eosinophil counts and the number of outcome events in the outcome period.

The primary definition of high blood eosinophil counts will be $\geq 0.45 \times 10^9$/L, based on previous work. Sensitivity analyses will be performed using $\geq 0.25$, $\geq 0.35 \times 10^9$/L and $\geq 0.55 \times 10^9$/L as cut-points.

Additional analyses will be performed to evaluate whether the MPR modifies the associations by including interaction terms of blood eosinophil counts and MPR into the regression model

(continuous or categorical depending on best model fit).
Analyses will be repeated in patients with good adherence, defined as MPR≥80%.

Sensitivity analyses will be performed for the full population after exclusion of patients with any diagnostic Read code for asthma recorded ever.
Additional analyses will be performed to study whether the associations are different in never-smokers and ex-smokers in the full populations.

Confounding will be evaluated by comparing the coefficients for the effect of high eosinophil counts on the outcome event in models with and without the variable included. A change in coefficient of ≥5% will be considered relevant.

Because there are patients with missing data on BMI and smoking habits, these variables are only kept in the model if there was relevant confounding.
In the case of relevant confounding by BMI or smoking habits, these variables are included as categorical variables with a separate category for patients with missing data. This procedure will be evaluated by comparing the coefficients for the effect estimate obtained from these models with those from a model analysing only patients with complete data available.

For the variable "age at index date" a categorical and a continuous variable (with evaluation of polynomial functions) are evaluated for best model fit and greatest confounding effect.

Final models will be arrived at following a forward-selection procedure, in which variables will be added one-by-one and were retained if the coefficient for the effect estimate (high eosinophil count) changed by ≥5%. Co-linearity will be checked by evaluating variance inflation factors (VIFs).

Comorbidities, which are univariately associated with blood eosinophil counts are evaluated for potential confounding effects separately as there are uncertainties about the underlying mechanism. These variables could be potential confounders if they are predictive of the occurrence of exacerbations through a mechanism other than the one under study. However, if they are intermediate factors on the causal pathway from high eosinophil counts to event occurrence, adjustment would be inappropriate. As these underlying mechanisms are unknown, effects of ≥5% on the effect estimate by adjustment will be separately reported.

### 3.4.2 Outcome analyses sub-study 2

The crude (unadjusted) risks of re-admission to hospital for COPD are reported in a life-table (Table 1) and Kaplan-Meier curves are constructed for the total population and for patients with and without high blood eosinophil counts for the maximum follow up period of 12 months after hospital discharge. Comparisons are made with a long-rank analysis.

Cox-proportional hazard regression with the time from hospital discharge date to the first re-admission date as the survival time, is performed to estimate HRs with 95% CI for the association between high blood eosinophil counts and time to re-admission over time periods

of 28 days, 12 weeks and 12 months, adjusted for potential confounders following the procedure as described for sub-study 1.

**Table 1. Example of a life-table describing the time at hospital re-admission, by blood eosinophil count**

| ***Number of patients with high blood eosinophil count*** | | | | | *Hazard probability* | *Survival probability* |
|---|---|---|---|---|---|---|
| *Weeks* | *At risk at start* | *Re-admission* | *Censored* | *Death* | | |
| 4 | | | | | | |
| 8 | | | | | | |
| 12 | | | | | | |
| 26 | | | | | | |
| 36 | | | | | | |
| 52 | | | | | | |
| ***Number of patients with normal blood eosinophil count*** | | | | | *Hazard probability* | *Survival probability* |
| *Weeks* | *At risk at start* | *Re-admission* | *Censored* | *Death* | | |
| 4 | | | | | | |
| 8 | | | | | | |
| 12 | | | | | | |
| 26 | | | | | | |
| 36 | | | | | | |
| 52 | | | | | | |
| ***Total population*** | | | | | *Hazard probability* | *Survival probability* |
| *Weeks* | *At risk at start* | *Re-admission* | *Censored* | *Death* | | |
| 4 | | | | | | |
| 8 | | | | | | |
| 12 | | | | | | |
| 26 | | | | | | |
| 36 | | | | | | |
| 52 | | | | | | |

### 3.4.3 Outcome analyses sub-study 3

Means of the number of events per person year of follow up with standard deviations (SD) will be reported for count variables next to distributions (number and percentage) of categorical variables describing HRU in the baseline and outcome year. HRU events recorded at the index date are included in the baseline year, except medication prescriptions for which prescriptions at the index date are included in the outcome year.

Costs will be described as means with standard deviations. Costs of 4 subgroups of patients on Triple therapy at high risk of exacerbations will be compared with overall mean costs of patients with COPD in the total population by calculation of costs ratios with 95% confidence intervals, estimated by 1000 bootstrap replicates.
Non-parametric Mann-Whitney tests are performed to test differences in average costs between different populations of patients.

### 3.4.4 Outcome analyses sub-study 4

Two one or two-step generalized linear models with gamma distribution and log link will be used to perform regression analysis with total all-cause and total COPD-related costs as the outcome variables.

Univariate analyses will be performed to estimate unadjusted associations for all candidate predictors of total costs (see paragraph 3.3.3 for list).

All candidate predictors will be fed into a multiple regression analysis with backwards selection of the model with the best fit, based on Akaike's information criterion (AIC).
An interaction term of blood eosinophil counts and smoking status will be included in the model as potential predictor next to the main effects to evaluate relevant modification of the independent effect of blood eosinophil counts by different smoking habits.

Relative costs adjusted for other predictors will be estimated from the model for patients with and without high blood eosinophil counts.

## 3.5 Bias

### 3.5.1 Methods to Minimize Bias

Analyses will be adjusted for all potential confounders of the associations by multiple regression analysis.

### 3.5.2 Limitations

1. 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.
2. Exposure to drugs is estimated based on the number of prescribed doses over time periods, which does not guarantee correct use of all doses included.
3. OPCRD doesn't provide detailed information on GP consultations. The number of GP consultations may therefore be overestimated.
4. Although full blood count measurements are part of the routine work up in Primary Care for patients with COPD, patients with blood eosinophil counts available may not be representative of the total population of COPD patients.

## 3.6 Sample Size and Power Calculations

### 3.6.1 Sub-study 1

Figure 6 shows that 1,645 patients are required for each therapy group to find a significant (α=0.05) Rate Ratio of 1.3 as previously found with 80% power, when analysing the association between high blood eosinophil counts and the number of exacerbations, assuming 10% of patients having high blood eosinophil counts and mean rate of events of 0.68 in patients without high blood eosinophil counts as previously observed.

Table 2 shows the proportions of COPD patients on different treatment options in a previous study of OPCRD patients with COPD.

**Table 2. Frequencies of therapy options in a previous OPCRD study of patients with classical COPD**

| Therapy option | Frequency (%) in classical COPD patients |
|---|---|
| SABA and/or SAMA | 18 |
| LAMA and / or LABA | 11 |
| ICS / LABA combined | 17 |
| Triple therapy | 14 |

Around 46,000 COPD patients from OPCRD are estimated to be available for analyses of whom one third is expected to be an active smoker. Thus, 5,000 to 8,000 OPCRD patients are estimated to be available for each treatment group of whom 3,400 to 5,500 are not active smokers.

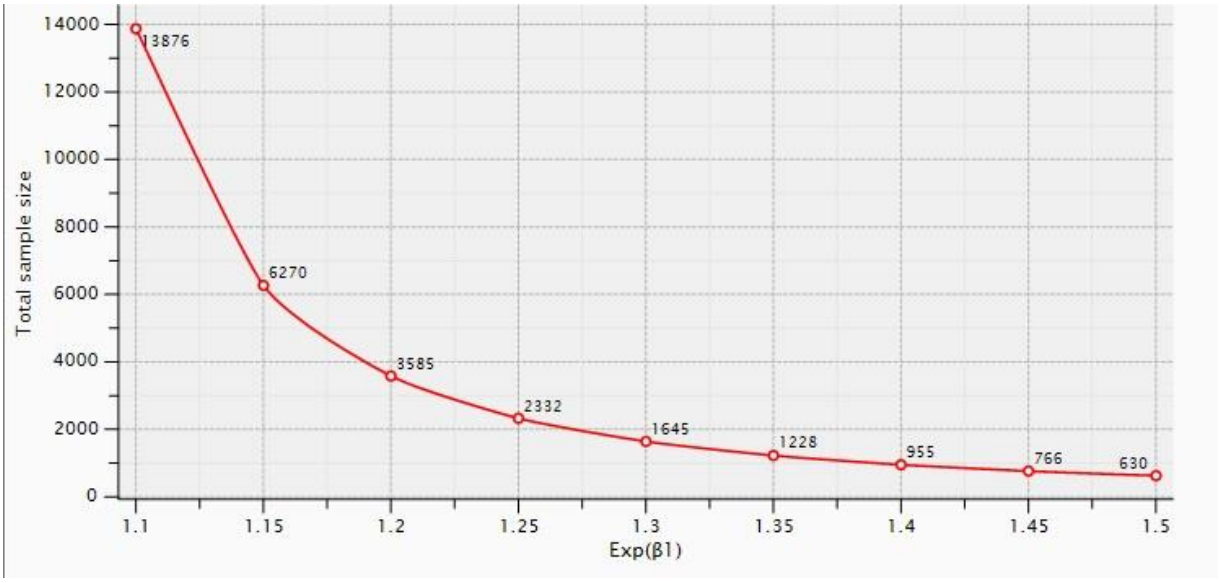



**Figure 6. Total sample size (Y-axis) required for finding different Rate Ratio's (X-axis) significant with 80% statistical power, assuming a mean rate of events of 0.68 in patients without high blood eosinophil counts and a prevalence of 10% of high blood eosinophil counts**

### 3.6.2 Sub-study 2

A recent study performed in Scotland found hospital admission rates of 127 per 1,000 patient years for COPD exacerbations at any diagnostic position (24). In that study, 10% of re-admission occurred within 14 days.

Around 10,000 patients with a blood eosinophil count available within one year prior to a hospital admission for COPD recorded in HES are required for finding a hazard ratio of 1.3 significant ($\alpha$=0.05), assuming a baseline re-admission risk of 10% and 10% of patients having high blood eosinophils (Table 3).

Table 3. Numbers needed for finding different Hazard Ratio's

| **Hazard Ratio high vs normal** | **Re-admission risk in patients with normal eosinophil counts** | **Prevalence of high eosinophil count** | **Total number of COPD patients required** | **Numbers needed normal / high** | **Power at $\alpha$=0.05** |
|---|---|---|---|---|---|
| **1.4** | 10% | 10% | 5,729 | 5,161 / 568 | 80% |
| **1.3** | 10% | 10% | 10,079 | 9,080 / 999 | 80% |
| **1.2** | 10% | 10% | 22,442 | 20,218 / 2224 | 80% |

### 3.6.3 Sub-study 3

Table 2 shows that 14% of patients are estimated to be on triple therapy of whom 25% is estimated to have a history of 2 or more exacerbations in the past 12 months or >1 hospitalisation. Thus, around 3.5% of patients are expected to be available for analyses on the association between high blood eosinophil counts and HRU / costs of whom 57% will not be actively smoking.

A total number of 979 patients on Triple Therapy with 2 or more exacerbations in the baseline year are required to find a 0.3 standard deviation greater amount of costs in patients with high blood eosinophil counts compared with patients with normal counts (Figure 7).

### 3.6.4 Sub-study 4

Figure 7 shows that a total number of 2,200 patients are required to find a difference of 0.2 standard deviations in logarithmically transformed costs between groups with and without high blood eosinophil counts with 80% power (α=0.05), assuming a frequency of 10% for blood eosinophilia.

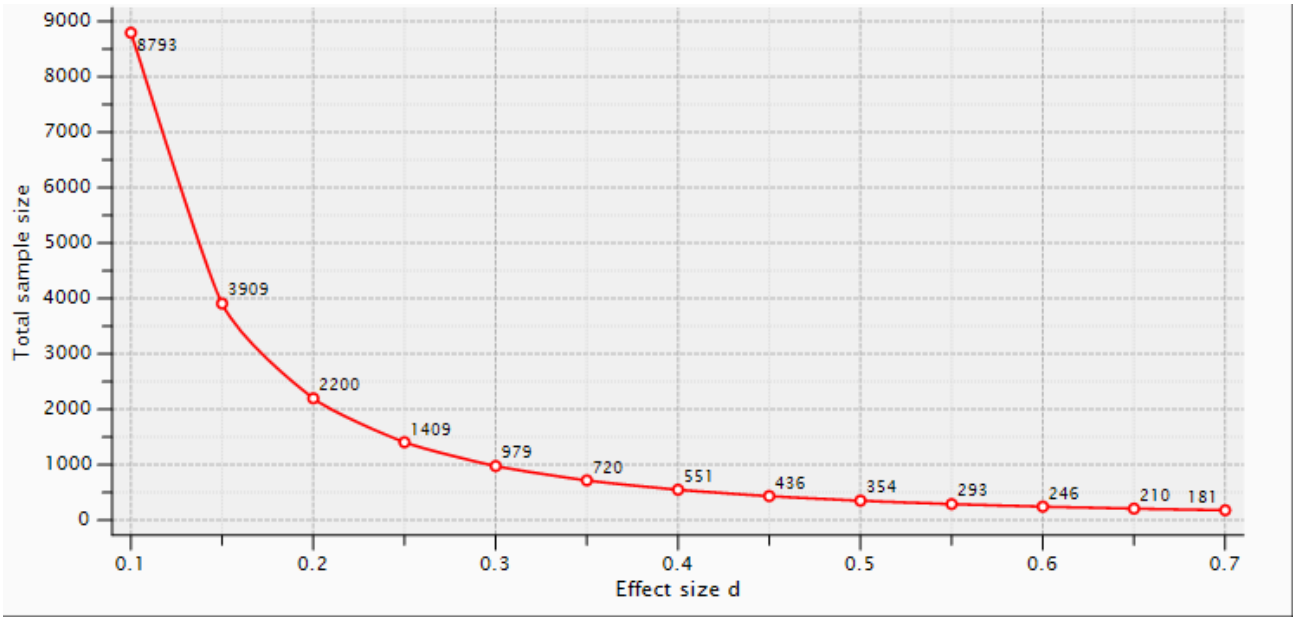



**Figure 7. Total number of patients required (Y-axis) to find standardised differences in logarithmically transformed costs between groups with and without high blood eosinophils**

# 4. STUDY CONDUCT AND REGULATORY DETAILS

## 4.1 Data Management

CPRD data are delivered by AZ through their license if required.
Database construction and analyses of data will be performed by OPRI.

### 4.1.1 Estimated Study Timelines

| Timelines For Study Stages | Date |
|---|---|
| ~~First draft protocol and statistical analyses delivery to AZ~~ | ~~11/10/2016~~ |
| ~~Review first draft protocol and statistical analysis plan by AZ~~ | ~~25/10/2016~~ |
| Revised Protocol to AZ / SC | 21/11/2016 |
| Review revised protocol by AZ / SC | 1/12/2016 |
| Protocol sign-off / submission ADEPT (and ISAC) applications | 5/12/2016 |
| **Report sub-study 1 delivery AZ** | **22/12/2016** |
| Report sub-study 1 reviewed by AZ | 06/01/2017 |
| Report sub-study 1 for SC review | 13/01/2017 |
| **Draft abstract sub-study 1 ERS delivery AZ** | **16/01/2017** |
| **Report sub-study 2 delivery AZ** | **23/01/2017** |
| Review report sub-study 1 by SC | 30/01/2017 |
| Draft abstract 1 ERS for SC review | 09/02/2017 |
| **Abstracts submission ERS** | **Deadline ERS** |
| Report sub-study 2 reviewed by AZ | 09/03/2017 |
| Report sub-study 2 for SC review | 16/03/2017 |
| **Report sub-studies 3 &4 delivery AZ** | **16/03/2017** |
| Report sub-studies 3 & 4 reviewed by AZ | 13/04/2017 |

| | |
|---|---|
| Report sub-studies 3 & 4 for SC review | 18/04/2017 |
| **Manuscript 1 first draft** | **06/03/2017** |
| Report sub-studies 3 & 4 reviewed by SC | 08/05/2017 |
| Final report delivery | 16/05/2017 |
| **Manuscript 2 first draft** | **06/07/2017** |
| Draft abstracts 3 & 4 ATS delivery AZ | 05/10/2017 |
| Draft abstracts 3 & 4 ATS for SC review | 20/10/2017 |
| **Abstract submission ATS 2018** | **Deadline ATS** |

## 4.2 Protection of Human Subjects

The Non-Interventional Study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, ICH GCPs, GPP and the applicable legislation on Non-Interventional Studies.

The Investigator will perform the NIS in accordance with the regulations and guidelines governing medical practice and ethics in the country of the NIS and in accordance with currently acceptable techniques and know-how.

The final protocol of the Non-Interventional Study, including the final version of the Subject Informed Consent Form, must be approved or given a favourable opinion in writing by the Ethics Committee/Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

The Ethics Committee/IRB/IEC must also approve any amendment to the protocol and all advertising used to recruit subjects for the study, according to local regulations. >>

## 4.3 Communication Plan

### 4.3.1 Publication Plan

Publication plans will be discussed with AZ after the reports have been delivered.
The aim is to publish the results in at least two manuscripts. Abstracts of the results of each objective will be submitted to international conferences, preferably the ERS and ATS conferences in 2017

### 4.3.2 Compliance with Study Registration and Results Posting Requirements

The study will be registered at ENCePP (http://www.encepp.eu/)

### 4.3.3 Compliance with Financial Disclosure Requirements

Any information that may be seen as a conflict of interest in terms of compensation or financial interests will be disclosed for each investigator.

# 5. LIST OF REFERENCES

1. Singh D, Kolsum U, Brightling CE, Locantore N, Agusti A, Tal-Singer R. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. The European respiratory journal. 2014;44(6):1697-700.
2. Brusselle G, Price D, Gruffydd-Jones K, Miravitlles M, Keininger DL, Stewart R, et al. The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK. Int J Chron Obstruct Pulmon Dis. 2015;10:2207-17.
3. Shah T, Press VG, Huisingh-Scheetz M, White SR. COPD Readmissions: Addressing COPD in the Era of Value-Based Healthcare. Chest. 2016.
4. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. Lancet Respir Med. 2015;3(6):435-42.
5. Watz H, Tetzlaff K, Wouters EF, Kirsten A, Magnussen H, Rodriguez-Roisin R, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. Lancet Respir Med. 2016;4(5):390-8.
6. Bafadhel M, McKenna S, Terry S, Mistry V, Pancholi M, Venge P, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. Am J Respir Crit Care Med. 2012;186(1):48-55.
7. Prescribing and Primary Care Services HaSCIC. Quality and Outcomes Framework – Prevalence, Achievements and Exceptions Report, England 2013-14. 2014.
8. British Lung Foundation. Chronic Obstructive Pulmonary Disease (COPD) Statistics (https://statistics.blf.org.uk/copd). June 2016.
9. Pavord ID, Lettis S, Locantore N, Pascoe S, Jones PW, Wedzicha JA, et al. Blood eosinophils and inhaled corticosteroid/long-acting beta-2 agonist efficacy in COPD. Thorax. 2016;71(2):118-25.
10. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir Med. 2015;3(11):849-58.
11. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. Am J Respir Crit Care Med. 2016;193(9):965-74.
12. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016. Available from: http://www.goldcopd.org/.
13. Barnes NC, Sharma R, Lettis S, Calverley PM. Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. The European respiratory journal. 2016;47(5):1374-82.
14. Mattishent K, Thavarajah M, Blanco P, Gilbert D, Wilson AM, Loke YK. Meta-review: adverse effects of inhaled corticosteroids relevant to older patients. Drugs. 2014;74(5):539-47.

15. Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. The American journal of medicine. 2010;123(11):1001-6.
16. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax. 2013;68(11):1029-36.
17. Price DB, Russell R, Mares R, Burden A, Skinner D, Mikkelsen H, et al. Metabolic Effects Associated with ICS in Patients with COPD and Comorbid Type 2 Diabetes: A Historical Matched Cohort Study. PloS one. 2016;11(9):e0162903.
18. Duman D, Aksoy E, Agca MC, Kocak ND, Ozmen I, Akturk UA, et al. The utility of inflammatory markers to predict readmissions and mortality in COPD cases with or without eosinophilia. Int J Chron Obstruct Pulmon Dis. 2015;10:2469-78.
19. Bass DA, Gonwa TA, Szejda P, Cousart MS, DeChatelet LR, McCall CE. Eosinopenia of acute infection: Production of eosinopenia by chemotactic factors of acute inflammation. The Journal of clinical investigation. 1980;65(6):1265-71.
20. Hospers JJ, Schouten JP, Weiss ST, Postma DS, Rijcken B. Eosinophilia is associated with increased all-cause mortality after a follow-up of 30 years in a general population sample. Epidemiology (Cambridge, Mass). 2000;11(3):261-8.
21. BMA. General Medical Services (GMS) Quality and Outcomes Framework, Guidance for GMC Contract 2015/2016. (British Medical Association and NHS Employers, 2015. 2015.
22. Centre NCG. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care London: National Clinical Guideline Centre. Available from: http://guidance.nice.org.uk/CG101/Guidance/pdf/English. National Clinical Guideline Centre; 2010.
23. Terradas R, Grau S, Blanch J, Riu M, Saballs P, Castells X, et al. Eosinophil count and neutrophil-lymphocyte count ratio as prognostic markers in patients with bacteremia: a retrospective cohort study. PloS one. 2012;7(8):e42860.
24. Hunter LC, Lee RJ, Butcher I, Weir CJ, Fischbacher CM, McAllister D, et al. Patient characteristics associated with risk of first hospital admission and readmission for acute exacerbation of chronic obstructive pulmonary disease (COPD) following primary care COPD diagnosis: a cohort study using linked electronic patient records. BMJ open. 2016;6(1):e009121.

# 6. APPENDICES

## 6.1 ICD-10 CM codes for COPD

J40 Bronchitis, not specified as acute or chronic
J410 Simple chronic bronchitis
J411 Mucopurulent chronic bronchitis
J418 Mixed simple and mucopurulent chronic bronchitis
J42 Unspecified chronic bronchitis
J430 Unilateral pulmonary emphysema [MacLeod's syndrome]
J431 Panlobular emphysema
J432 Centrilobular emphysema
J438 Other emphysema
J439 Emphysema, unspecified
**J440 Chronic obstructive pulmonary disease with acute lower respiratory infection**
**J441 Chronic obstructive pulmonary disease with (acute) exacerbation**
J449 Chronic obstructive pulmonary disease, unspecified