Burden of severe uncontrolled eosinophilic asthma in the UK population

Historical follow-up study on CPRD and OPCRD to establish the burden of severe uncontrolled eosinophilic asthma in the UK

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
A&E	Accident & Emergency
AZ	AstraZeneca
BDP	Beclomethasone Dipropionate
CCI	Charlson Comorbidity Index
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
FEV_1	Forced Expiratory Flow in one second
GP	General Practitioner
HES	Hospital Episode Statistics
HFA	Hydrofluoralkane propellant
HRG	Healthcare Resource Group
HRU	Healthcare Resource Utilisation
ICS	Inhaled Corticosteroids
ICU	Intensive Care Unit
IQR	Interquartile range
IL-5	Interleukin-5
ICU	Intensive Care Unit
LABA	Long Acting Beta-Agonists
LAMA	Long-acting Muscarinic Antagonists
LTRA	Leukotriene Receptor Antagonists
mAb	Monoclonal antibody
µg	Microgram
MPR	Medication Possession Ratio
ONS	Office for National Statistics
OPC	Optimum Patient Care
OPCRD	Optimum Patient Care Research Database
PEF	Peak Expiratory Flow
PSSRU	Personal Social Services Research Unit
QOF	Quality Outcomes Framework
RDAC	Risk Domain Asthma Control

RiRL	Research in Real Life
SABA	Short Acting Beta-Agonists

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PROTOCOL SYNOPSIS

Historical follow-up study on CPRD and OPCRD to establish the burden of severe uncontrolled eosinophilic asthma

Background/Rationale:

Benralizumab is a monoclonal antibody against the Interleukine-5 receptor, currently undergoing phase 3 clinical trials for use in the treatment of asthma. This therapy is being developed by AstraZeneca (AZ). Benralizumab will target patients with severe, uncontrolled eosinophilic asthma treated with high-dose inhaled corticosteroids (ICS) and long-acting beta2-agonist (LABA).
There is a need to establish the proportion of patients with severe uncontrolled eosinophilic asthma among asthma patients who would be eligible to be treated with benralizumab and to describe their burden of illness and healthcare resource utilisation (HRU).

Objectives:

The first objective of the study is to describe the distribution of asthma severity and control, treatment status, blood eosinophilia and their combinations and to establish the proportion of patients with severe uncontrolled eosinophilic asthma among asthma patients with blood eosinophil measurements available and its subgroups.
The second objective will be to assess the rate of exacerbations and HRU during a follow-up year among patients with severe uncontrolled eosinophilic asthma and its subgroups and in the total population of asthma patients who have had eosinophil counts.

Methods:

Study design: A historical follow-up study will be performed among the UK population of patients with active asthma extracted from OPCRD and CPRD at the last recorded blood eosinophil count (index date).
One year of continuous records prior to the index date will be used for baseline characterisation of patients with asthma and for assessment of patients with severe uncontrolled eosinophilic asthma. Burden of disease and HRU associated with severe uncontrolled eosinophilic asthma will prospectively be assessed in the year after the index date (outcome year).

Data Source(s): A combined dataset of patients with asthma using data extracted from OPCRD and CPRD will be used for analyses. CPRD data will be linked to HES statistics to describe frequencies of hospitalisations and outpatient attendances.

Methods of analysis:
The distribution of asthma severity and control, treatment status, blood eosinophilia, other asthma determinants and their combinations will be described in the baseline year prior to the index date in the total population and stratified by four age groups and the presence of blood eosinophilia using four cut-off values.
The rate of exacerbations and HRU will be described in the outcome year in patients with severe uncontrolled eosinophilic asthma, defined as patients with blood eosinophilia, treated with high dose ICS + LABA who had ≥2 exacerbations in the baseline year.
All analyses are performed in patients with and without an overlapping diagnosis of COPD separately.

MILESTONES

Date	Milestone
19/6/2015	AZ Sign-off protocol
18/12/2015	Delivery of report Objective 1: Baseline characterisation
11/3/2016	Delivery of Objectives 2: Prospective burden and HRU
1/6/2016	Proposal manuscript outline
1/8/2016	Manuscript delivery first draft
16/9/2016	Manuscript submission

1. BACKGROUND AND RATIONALE

1.1 Background

Although the majority of asthma patients can be effectively treated with currently available medications, a substantial subset of patients exists who remain difficult-to-treat[1]. These patients account for a relatively large proportion of healthcare resource expenditure[1].

In both developed and developing countries, patients with severe asthma have been estimated to be responsible for approximately 50% of all direct and indirect costs associated with asthma, even though this patient population represents just 10 to 20% of all asthma patients[2].

Several studies have tried to identify subgroups of asthma patients with severe asthma and have recognised late-onset eosinophilic asthma as an important phenotype different to early-onset atopic asthma[1].

Eosinophils play an important role in the inflammation of the airways observed in patients with asthma. Blood eosinophil levels have been shown to correlate with asthma severity[3].

Low-dose inhaled corticosteroids remain the treatment of choice in most asthma. Although inhaled and/or systemic corticosteroids are initially effective in controlling eosinophilic asthma in many patients, resistance and toxicity become increasingly common over time and second-line agents are often needed[4].

Biological therapies are already available and are considered useful as an add-on treatment for severe asthma which is inadequately controlled by corticosteroids[4]. Xolair® (omalizumab), a monoclonal immunoglobulin-E-targeted antibody produced by Novartis, was the first biological therapy approved to treat asthma with a specific focus on patients with evidence of atopy as underlying mechanism[5].

Drugs that target eosinophils and especially interleukin-5 (IL-5) may be an ideal mean for the treatment of eosinophilic asthma as IL-5 plays an important and specific role in the differentiation and activation of eosinophils[6]. Humanised monoclonal antibodies (mAbs) that specifically bind IL-5 with high affinity have been developed to target patients with treatment-refractory asthma. Both mepolizumab (GlaxoSmithKline) and reslizumab (Teva Pharmaceuticals) have demonstrated to be effective in the treatment of poorly controlled eosinophilic asthma despite treatment with inhaled corticosteroids[4].

Benralizumab, developed by AstraZeneca (AZ), is an investigational mAb that binds to the α-chain of the IL-5 receptor. It is currently undergoing phase 3 clinical trials for use in the treatment of asthma[7,8].

1.2 Rationale

There is a need to establish the proportion of patients with asthma who would be classified as having severe uncontrolled eosinophilic asthma in the general population. Furthermore, information is needed to establish the burden and costs of disease associated with severe uncontrolled eosinophilic asthma that may be treated with benralizumab.

The aims of the study:

In a population of asthma patients who have had blood eosinophil counts measured, our aims are:

1. To describe the distribution of asthma severity and control, treatment status, blood eosinophilia and other asthma determinants
2. To determine the proportion of patients with severe uncontrolled eosinophilic asthma who would be eligible for treatment with benralizumab
3. To quantify the disease burden and healthcare resource utilisation (HRU) associated with severe uncontrolled eosinophilic asthma

2. OBJECTIVES

2.1 First Objective

The first objective of the study is to describe the distribution of asthma severity and control, treatment status, blood eosinophilia, other asthma determinants and/or their combinations and to establish the proportion of patients with severe uncontrolled eosinophilic asthma among asthma patients who have had blood eosinophil counts and its subgroups.

2.2 Second Objective

The second objective is to assess the rate of exacerbations and healthcare resource utilisation (HRU) during a follow-up year among patients with severe uncontrolled eosinophilic asthma and in the total population of asthma patients who have had eosinophil counts and its subgroups.

3. METHODOLOGY

3.1 Study Design – General Aspects

A historical follow-up study will be performed among the UK population of patients with asthma using a combined dataset extracted from the Clinical Practice Research Datalink (CPRD) and the Optimum Patient Care Research Database (OPCRD) using the date of the last recorded blood eosinophil count measurement as the index date.

Data from CPRD will be pooled with data from OPCRD to provide sufficient data to study the relatively small population of patients with severe uncontrolled eosinophilic asthma and its subpopulations.

Two datasets will be constructed separately using CPRD and OPCRD data in a patient unidentifiable form with harmonised variables. The datasets are checked for overlapping data for the purpose of exclusion of duplicate data by matching on a number of variables, such as the year of birth, gender and date of the last blood eosinophil count. During this process patients will never become identifiable. In case of duplicate data, data are used from CPRD.

One year of continuous records prior to the index date will be extracted for baseline characterisation (patient demographics, co-morbidities, asthma severity and control, treatment status, blood eosinophilia, other asthma determinants and their combinations).
Patients with severe uncontrolled eosinophilic asthma will be assessed in the year prior to the index date (baseline year).
Outcomes for the second objective (number of exacerbations, HRU and associated costs) will be assessed in the year after the index date (outcome year) in these patients and in the total population of asthma patients (Figure 1).

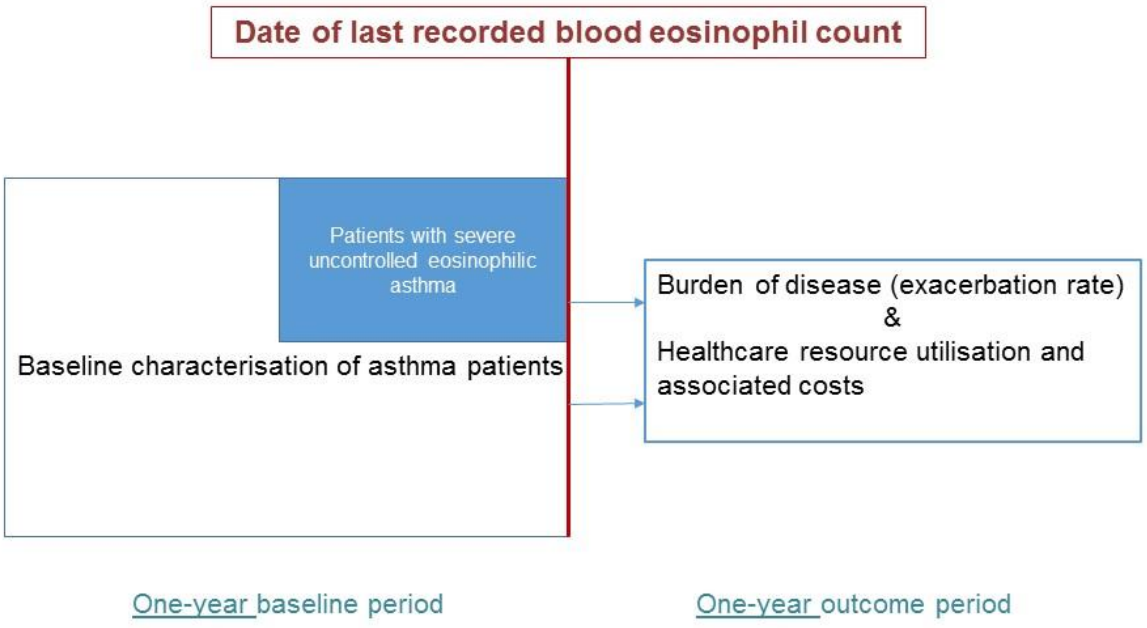

Figure 1. Study design

3.1.1 Data Source(s)

The following data sources will be combined to select patients with asthma:

A. Clinical Practice Research Datalink (CPRD)

The Clinical Practice Research Datalink (CPRD) is a large computerised 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.

CPRD data will be linked to Hospital Episode Statistics (HES)
Analyses requiring information on hospitalisation and outpatient visits will be performed in a subgroup of patients from CPRD who have HES data available. In general, HES provides more complete and reliable detailed information on hospitalisation and outpatient visits than

GP records.
Healthcare Resource Groups (HRGs) codes, standard groupings of clinically similar treatments which use common levels of healthcare resource, will also be extracted from HES.

B. Optimum Patient Care Research Database (OPCRD)

The OPCRD comprises data captured through the Optimum Patient Care (OPC) clinical service evaluation. OPC is a not-for-profit organisation that offers free respiratory clinical evaluations for primary care practices. The clinical evaluation involves a review of (anonymised) Electronic Medical Records and also responses to disease-specific questionnaires. OPC evaluates the anonymous patient-level data (objective and subjective combined) to assess each patient's asthma control, severity and risk, and makes guideline-based recommendations for possible management changes, where appropriate. OPCRD contains all the anonymised data captured through the OPC service and has been approved for clinical research use by the Trent Multicentre Research Ethics Committee (Trent MREC).

Analyses requiring questionnaire data on pack years of smoking and absence from work / school due to asthma will be performed in a subgroup of patients from OPCRD with questionnaire data available.

3.2 Study Population

All patients with active asthma and ≥1 blood eosinophil count available will be selected from CPRD and OPCRD.
Outcomes describing asthma exacerbations and control are additionally described in patients from CPRD who have Hospital Episode Statistics (HES) data available.

The analyses will be performed in two populations:

1. Asthma patients without an overlapping diagnosis of COPD
2. Asthma patients, aged ≥40 years with an overlapping diagnosis of COPD.

3.3 Selection Criteria*

1. No diagnostic Read code ever recorded for the following chronic lower respiratory conditions:
    a. Bronchiolitis Obliterans
    b. Lung disease due to external agents other than smoking, such as occupational agents
    c. Pulmonary fibrosis
    d. Pulmonary hypertension
    e. Cystic fibrosis

* Numbers will be described hierarchically in patient's flow chart

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2. A diagnostic Read code for asthma qualifying for inclusion in the register of patients with asthma, which GP practices in the UK maintain for the Quality Outcomes Framework† (see Appendix 8.1 and http://www.hscic.gov.uk/qof for details).
3. Age ≥ 5 years at the most recent asthma diagnosis
4. ≥ 1 prescription for asthma medication in the baseline year (see Appendix 8.1)
5. ≥ 1 valid blood eosinophil count measurement available (date is index date)
6. Valid continuous data for the study period, i.e. ≥1 year prior to index date for baseline characterisation and ≥1 year after index date for outcome measurements

An overlapping diagnosis of COPD will be defined as a diagnostic Read code for COPD qualifying for the inclusion in the register of patients with COPD, which GP practices in the UK maintain for the Quality Outcomes Framework. This requires a post-bronchodilator FEV_1/FVC <0.70 at diagnosis as from 2008.

† The Quality Outcomes Framework is the annual reward and incentive programme detailing GP practice achievement results

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

4.1 Variables to be described in baseline year

4.1.1 Baseline characteristics

The following characteristics will be described in the baseline year:

1. Demographics recorded closest to or at the index date: age, sex, body mass index (BMI) and smoking status (never, ex-smoker, current smoker and pack years‡ of smoking)

2. Comorbidities recorded ever:
    a. Allergic and non-allergic rhinitis
    b. Chronic sinusitis
    c. Eczema
    d. Nasal polyps
    e. Gastro-oesophageal reflux disease (GERD)
    f. Diabetes Mellitus type I and type II
    g. Osteopenia / Osteoporosis
    h. Hypertension
    i. Obstructive Sleep apnoea
    j. Cataract
    k. Cardiovascular disease
    l. Psychiatric conditions / Anxiety/ Depression
    m. Sleep disorders
    n. Chronic kidney disease
    o. Charlson Comorbidity Index (CCI) score

3. Two spirometry measurements will be described:
    a. Measurement closest to index date within 5 years prior to or after index date
    b. Measurement closest to index date performed in baseline year

    The following spirometry parameters will be described:

    a. Peak Expiratory Flow (PEF)
    b. Forced Expiratory Flow in one second (FEV_1)
    c. Bronchodilator reversibility of FEV_1,
        i. % change relative to pre-bronchodilator FEV_1 after bronchodilator
        ii. Reversibility (yes/no) defined as ≥12% change and at least 200 ml (adults)
    d. FEV_1/Forced Vital Capacity (FVC) ratio

‡ In patients from OPCRD with questionnaire data available only

4. Number of times full blood counts and blood eosinophil counts recorded during registration at practice.

4.1.2 Blood eosinophil counts

The distribution of blood eosinophil counts and blood eosinophilia at the last recorded blood count measured at any time[§] prior to the index date will be described using four definitions for eosinophilia:

1. ≥ 0.2 (or $\geq 0.15 \times 10^9$/L for measurements with 2 decimals available)
2. $\geq 0.3 \times 10^9$/L
3. $\geq 0.4 \times 10^9$/L
4. $\geq 0.5 \times 10^9$/L

4.1.3 Asthma exacerbations and control

Distributions of the following outcomes will be described in the baseline year:

1. Number of asthma exacerbations, defined by the ATS/ERS Task Force[9], as the occurrence of the following events (see Appendix 8.2.1 for detailed definition):
    a. Asthma-related hospital attendance / admission AND/OR
    b. A&E attendance AND/OR
    c. An acute oral corticosteroid course with evidence of a lower respiratory consultation
2. Number of acute oral corticosteroid courses with evidence of a lower respiratory consultation
3. Number of lower respiratory tract infections treated with antibiotics or a prescription for antibiotics with a lower respiratory Read code within a +/- 5 day window
4. Number of asthma-related hospital admissions and length of stay
5. Number of A&E attendances for asthma from GP database[**] / Number of day cases from HES
6. Number of outpatient visits for asthma
7. Asthma control:
    a. Risk Domain Asthma Control (RDAC), defined as the absence of the following aspects of asthma risk during the baseline year:
        i. Asthma-related A&E attendance, in-patient admission or unplanned asthma-related out-patient department attendance
        ii. Acute courses of oral corticosteroids with evidence of a lower respiratory consultation
        iii. Antibiotics prescribed with evidence of a lower respiratory consultation

[§] An explorative analysis will be performed to describe the distribution of the time difference between date of last recorded blood eosinophil count and the index date to decide whether a lower limit of the most recent date will be introduced to select patients with blood eosinophils available
[**] Information on A&E attendances from GP database will be limited.

b. Overall Asthma Control, defined as the absence of the following aspects of asthma risk during the baseline:
    i. Attainment of RDAC AND
    ii. Average daily dose of ≤200 µg salbutamol / ≤500 µg terbutaline

4.1.4 Asthma severity and treatment status

Distributions of the following outcomes will be described in the baseline year:

1. Daily dose[††] of ICS beclomethasone dipropionate (Clenil modulite) equivalent in µg/day
2. Low / medium / high daily dose of ICS following GINA guideline[10] (for definition see Appendix 8.3)
3. BTS high daily dose of ICS, defined as ≥800 µg/day BDP equivalent in adults; ≥400 µg /day in children aged 5–12 years (yes/no)
4. High daily dose ICS + LABA+/- additional controllers GINA definition (yes/no)
5. High daily dose ICS + LABA+/- additional controllers BTS definition (yes/no)
6. BTS and GINA steps of treatment (see Appendices 8.4 & 8.5 respectively)
7. Reliever medications: daily SABA dose (µg/day) (0,1-100, 101-200, 201-300, 301-400, >400)
8. Add-on treatment prescriptions (≥1 prescription in baseline year (yes/no) on top of ICS + LABA)):
    a. Omalizumab (Xolair®)
    b. Theophylline
    c. Leukotriene Receptor Antagonists (LTRA)
    d. Long-acting Muscarinic Antagonists (LAMA)
    e. LAMA + LABA combinations
9. Combinations of controller and/or reliever treatment (highest step in baseline year)
10. Maintenance (chronic) oral corticosteroid prescriptions
    a. Probable maintenance oral corticosteroids prescriptions (≥1 in baseline year (yes/no) [‡‡]
    b. Cumulative dose of systemic corticosteroids in the baseline year with average dose of ≥5 mg/day (yes/no)
11. ICS and ICS + LABA adherence, measured as:
    a. The number of canisters dispensed for 30 days in the baseline year (≥ 6, ≥9 (yes/no))
    b. ICS adherence, measured as Medication Possession Ratio (MPR) (=days of supply received divided by period of time in [years])(≥0.50, ≥0.70 (yes/no))

[††] Daily dose calculated as: (number of inhalers prescribed in baseline year * doses in pack) / 365) * mcg strength)
[‡‡] An algorithm will be used to define prescription of maintenance oral steroid (see appendix)

4.1.5 Combinations of asthma exacerbations and treatment

Distributions of the following outcomes will be described in the baseline year:

1. High dose ICS (≥800 µg/day BPD-CFC equivalent in adults; ≥400 µg/day in children 5-11 years) + LABA in combination with:
    a. ≥2 exacerbations in baseline year[§§]
    b. ≥4 exacerbations in baseline year[§§]
    c. ≥2 hospitalisations or ≥3 A&E attendance, including ≥1 hospitalisation
2. Maintenance oral corticosteroids or ≥4 exacerbations in baseline year

4.1.6 Severe uncontrolled eosinophilic asthma

Severe asthma is defined as asthma treated with ICS and LABA at high dose of ICS, i.e. ≥800 µg/day BDP-CFC equivalent for adults and ≥400 µg/day for children 5-11 years. Uncontrolled asthma is defined as having ≥ 2 asthma exacerbations in the baseline year. Eosinophilic asthma is defined as asthma with blood eosinophilia present at the index date using four definitions of eosinophilia.

Severe uncontrolled eosinophilic asthma will be defined using the following criteria:

1. Asthma diagnostic Read code AND
2. Age ≥ 5 years at the most recent asthma diagnosis AND
3. ≥ 2 asthma exacerbations in the year prior to index date (baseline year) AND
4. Prescription of ICS and LABA at a high dose of ICS, defined as ≥800 BDP-CFC equivalent (HFA) in adults; ≥400 in children 5-11 years
5. Blood eosinophilia at the last recorded blood count using four definitions:
    a. ≥ 0.2 x 10^9/L
    b. ≥ 0.3 x 10^9/L
    c. ≥ 0.4 x 10^9/L
    d. ≥ 0.5 x 10^9/L

4.2 Variables to be described in outcome year

4.2.1 Prospective burden of disease

1. Number of asthma exacerbations, defined by the ATS/ERS Task Force, as the occurrence of the following events (see Appendix 8.2.1 for detailed definition):
    a. Asthma-related hospital attendance / admission AND/OR
    b. A&E attendance AND/OR
    c. An acute oral corticosteroid course with evidence of a lower respiratory consultation

[§§] defined as the occurrence of the following events:
a. Asthma-related hospital attendance / admission AND/OR
b. A&E attendance AND/OR
c. An acute oral corticosteroid course with evidence of a lower respiratory consultation

2. Number of acute oral corticosteroid courses with evidence of a lower respiratory consultation

4.2.2 Prospective healthcare resource utilisation

4.2.2.1 Primary outcomes:

1. Physician office visits:
    a. Total number of General Practitioner (GP) surgery consultations
    b. Number of asthma-related GP consultations
2. Outpatient visits, based on GP records in CPRD/OPCRD
    a. Number of outpatient visits for asthma or lower respiratory conditions
3. A&E attendances, based on GP records in CPRD/OPCRD
    a. Number of asthma-related A&E attendances
4. Hospital admissions: number of hospital admissions for asthma based on:
    a. GP records in CPRD/OPCRD
    b. CPRD-HES:
        i. with asthma (ICD-10 J45/J46) as primary diagnosis
        ii. with asthma at any record
        iii. with respiratory conditions (ICD-10 J00-J99) as primary diagnosis
5. Length of stay (LOS), calculated from the day of admission to the day of discharge (CPRD-HES)
    a. Median and IQR of LOS
    b. Short-stay (1 night) hospitalisations CPRD-HES:
        i. All hospital admissions
        ii. with asthma (ICD-10 J45/J46) as primary diagnosis
        iii. with asthma at any record
        iv. with respiratory conditions (ICD-10 J00-J99) as primary diagnosis
    c. Long-stay (≥1 nights) hospitalisations CPRD-HES:
        i. All hospital admissions
        ii. with asthma (ICD-10 J45/J46) as primary diagnosis
        iii. with asthma at any record
        iv. with respiratory conditions (ICD-10 J00-J99) as primary diagnosis
    d. Number of day cases (0 nights) CPRD-HES:
        i. with asthma (ICD-10 J45/J46) as primary diagnosis
        ii. with asthma at any record
        iii. with respiratory conditions (ICD-10 J00-J99) as primary diagnosis
6. Number of asthma-related drug prescriptions:
    a. Inhaled corticosteroids (ICS)
    b. Fixed dose combinations of ICS + LABA
    c. Long-acting β2-agonists (LABA)
    d. Short-acting β2-agonists (SABA)
    e. Short-acting Muscarinic Antagonists (SAMA)
    f. Long-acting Muscarinic Antagonists (LAMA)
    g. Leukotriene receptor antagonists (LTRA)
    h. Theophylline

i. Omalizumab (Xolair®)
j. Oral corticosteroids
k. Antibiotics courses with evidence of lower respiratory consultation

4.2.2.2 Secondary outcomes:

Indirect costs associated with asthma will be studied in the subpopulation of patients from OPCRD with questionnaire data available by describing:

a. Annual days of asthma-related absence from work:
Answer to question: "In the last 12 months, how many days had you had off work /education because of asthma"
b. Annual days of asthma-related absence from school for children:
Answer to question: "In the last 12 months, how many days has your child missed school because of asthma"

4.2.3 Analysis describing prospective healthcare resource utilisation in patients with severe uncontrolled eosinophilic asthma using 3 other cut-points of uncontrolled asthma

The following HRU outcomes with associated costs will be described in the outcome year for patients with severe uncontrolled eosinophilic asthma, aged 12 years or older without concurrent COPD, using 3 other cut-points for the number of exacerbations in the baseline year

1. ≥ 3 exacerbations
2. ≥ 4 exacerbations
3. ≥ 5 exacerbations

Outcomes:

1. Number of acute oral corticosteroid courses with evidence of a lower respiratory consultation
2. Number of GP consultations for asthma or lower respiratory disease
3. Number of outpatient visits for asthma or lower respiratory disease
4. Number of asthma-related A&E attendances
5. Number of asthma-related hospital admissions
6. Number of short-acting β2-agonists (SABA)

5. ANALYSIS PLAN

5.1 Summary statistics

The following summary statistics will be calculated:

1. Frequency statistics for dichotomous variables: number and percentage
2. Frequency statistics for count variables in five categories (0, 1, 2, 3, ≥4): number and percentage
3. Mean (standard deviation), median (interquartile range) for continuous variables depending on whether the outcome variable is normally distributed

5.2 Estimation of costs

Associated costs will be estimated by multiplying HRU outcomes by the estimated average costs associated with the specific HRU outcome (in GBP):

5.2.1 Primary care consultations

Primary care consultations are assumed to be G.P. lead except for asthma reviews, generally performed by nurses.
For cost calculations of primary care consultations performed by a GP, we assume that all GP consultations are of average duration (11.7 minutes).
Prices assigned to primary care consultation costs will be taken from the latest Personal Social Services Research unit (PSSRU) document (pages 192-195 of the current version) (http://www.pssru.ac.uk/project-pages/unit-costs/2015/

- The unit cost of A&E attendances is calculated as the weighted average of a category 2 investigation with a category 3 treatment and a category 1 investigation with a category 3-4 treatment. These were based on the dominant treatment being a nebuliser and some patients requiring further diagnostic testing.
- Prices assigned to secondary care costs will be based on the national average hospital costs as found on page 107 of the current PSSRU document from 2015
- Asthma-related inpatient visits are priced as non-elective admissions using the weighted average of Healthcare Resource Group (HRG) codes DZ15 following the 'NHS Reference cost schedule', prepared by the Department of Health , assigned from 2014-15
- Prices assigned to drugs will be taken from the Dictionary of Medicines and Devices browser (http://dmd.medicines.org.uk/)

5.3 Patient populations for descriptive analyses

All analyses will be performed in patients with and without an overlapping diagnosis of COPD separately. Analyses in the group of patients without overlapping COPD will be performed in the total group and in four age groups separately: 5-11, 12-17, 18-64, ≥65 years.

5.3.1 Patient populations for description of baseline characteristics

Baseline characteristics (outcomes paragraph 4.1.1) will be described in the total population of asthma patients and stratified by the presence or absence of eosinophilia, defined as ≥0.3 x $10^{9/}$L in the combined OPCRD /CPRD dataset.

5.3.2 Patient populations for description of blood eosinophils

The distribution of blood eosinophil counts (outcome paragraph 4.1.2) will be described in asthma patients from OPCRD /CPRD with and without overlapping COPD.

In addition the prevalence of eosinophilia will be described by GINA steps of treatment and combinations of GINA treatment steps with the number of exacerbations:

1. ≥4 exacerbations versus <4 exacerbations
2. ≥2 exacerbations versus <2 exacerbations

5.3.3 Patient populations for description of asthma control, severity and treatment status in the baseline year

Outcomes listed in paragraphs 4.1.3 to 4.1.5 will be described in patients from the combined OPCRD /CPRD dataset. Outcomes describing asthma exacerbations and control requiring information on hospitalisation or outpatient visits are additionally described in patients from CPRD with HES data available.

Outcomes will be additionally be described in:

1. Patients with blood eosinophil count <0.2 vs ≥0.2 x 10^9 /L
2. Patients with blood eosinophil count <0.4 vs ≥0.4 x 10^9 /L
3. Patients with blood eosinophil count <0.5 vs ≥0.5 x 10^9 /L

5.3.4 Patient populations for description of proportion with severe uncontrolled eosinophilic asthma

The number and proportion of patients fulfilling the criteria for the definition of severe uncontrolled eosinophilic asthma (paragraph 4.1.6) will be described in the total group of asthma patients. Results will be presented for patients from the combined OPCRD /CPRD dataset using four different definitions of blood eosinophilia: ≥0.2, ≥0.3, ≥0.4 and ≥0.5 x 10^9/L.

5.3.5 Patient populations for prospective burden of disease and HRU in the outcome year

Outcomes of prospective burden of asthma and HRU (Paragraphs 4.2.1 and 4.2.2) and associated costs will be described in the following populations:

1. Total population of asthma patients and stratified by age groups
2. Total population of asthma patients without concurrent COPD and stratified by age groups
3. Asthma patients with concurrent COPD, aged ≥40 years
4. Patients with severe uncontrolled eosinophilic asthma without concurrent COPD, aged ≥12 years who had ≥2 exacerbations in the baseline year, with ICS and LABA prescribed at a high dose of ICS, defined as a cumulative dose of ≥800 BDP-CFC equivalent (HFA) in both the baseline and the outcome year, using 4 cut-points of blood eosinophilia
5. Asthma patients with concurrent COPD, aged ≥40 years, with ICS and LABA prescribed at a high dose of ICS, defined as a cumulative dose of ≥800 BDP-CFC equivalent (HFA) in both the baseline and the outcome year, using 4 cut-points of blood eosinophilia

Outcomes of paragraph 4.2.3 will be described in the outcome year for asthma patients without concurrent COPD, aged ≥12 years who are adherent to high dose ICS and LABA in both baseline and outcome year in the subgroups described in the following table:

Exacerbations*** in the previous year to index	Eosinophil count at index			
	$\geq 0.2 \times 10^9$/L	$\geq 0.3 \times 10^9$/L	$\geq 0.4 \times 10^9$/L	$\geq 0.5 \times 10^9$/L
≥3	N	N	N	N
≥4	N	N	N	N
≥5	N	N	N	N

*** Number of asthma exacerbations, defined by the ATS/ERS Task Force[9], as the occurrence of the following events (see Appendix 8.2.1 for detailed definition):

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

5.3.6 Patient populations for indirect costs in outcome year

Indirect costs will be described in the total OPCRD population of asthma patients who have questionnaire data available and in patients with severe uncontrolled eosinophilic asthma using four definitions of blood eosinophilia: ≥0.2, ≥0.3, ≥0.4 and and ≥0.5 x 10^9/L.

6. 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. Full blood count measurements to be used to assess eosinophilia are generally requested for a specific medical reason and bias of results caused by this cannot be excluded. Asthma patients with blood eosinophil counts available may not be representative of the total population of asthma patients.
3. Although sputum eosinophilia has been shown to be a consistent feature in patients with difficult-to-treat asthma despite treatment with high doses of corticosteroids[11], blood eosinophilia may be less consistent. A large time window between assessment of blood eosinophilia and outcome measurements may influence the results.
4. The availability of data to study indirect costs related to severe uncontrolled eosinophilic asthma is very limited.
5. There is a low level of specific coding in HES which may limit the identification of all A&E attendances.
6. Lung function will be obtained without central quality control, so FEV_1, FVC and other indices collected in primary and secondary care might have high noise and variability

6.1 Communication Plan

6.1.1 Publication Plan

The results will be presented at least in one national/international conference and a manuscript will be submitted to a journal.

7. LIST OF REFERENCES

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8. APPENDICES

8.1 Quality Outcomes Framework Read codes for inclusion in the study population[†††]

Code criteria	*Qualifying diagnostic codes*	
Included	*Read codes v2*	*CTV3*
	H33..% (excluding H333.), H3120, 173A.	H33..% (excluding H44..%, H441., H440.%, X1025%, X1023, XaKdk, XaJFG, Xa1hD) X1020
	(Asthma diagnosis codes)	
Excluded	*Read codes v2*	*CTV3*
	21262 212G.	21262
	(Codes for asthma resolved)	

[†††] From the QOF Asthma ruleset_v31.0

	Read codes v2	*CTV3*
Required	c1... – c15z. c19..% c1B.. – c1EE. c1b..% c2...% (Excluding c23..%, c24..%) c3...% (Excluding c32..%) c4...% (Excluding c42..%, c44..%) c5...% (Excluding c52..%) c6...% c7...% cA...% ck1..%	c1...% (Excluding c16..%, x01Cn%, x01Co%, x01Ct%, x01Df%, x01Cp%) x02IG% c221., c222., c224., c226., c227. c31..% (Excluding l863.%, l861.%, l865., l866.) c33..% c41..% c43..% c51G., c51H., c51n. c64..% c69..% c6A..% c6B..% cA...% x01EF% c71..% x02LJ% (Excluding k6k1.%, l89.., k6k..) x01EJ% (Excluding k6e1.%, l891.%, k6e.., l89..) ck1..% c341. c342.
	(*Asthma-related drug treatment codes*)	

8.2 Definitions asthma control

8.2.1 Asthma exacerbation:

Exacerbations are defined by the ATS/ERS Task Force[9] as the occurrence of the following events:

a. Asthma-related hospital attendance / admission[11] AND/OR
b. A&E attendance AND/OR
c. An acute oral corticosteroid course with evidence of a lower respiratory consultation

8.2.2 Endpoints for asthma control:

A. Risk Domain Asthma Control (RDAC)

Controlled asthma is defined here as the absence of the following aspects of asthma risk during the outcome year:

a. Asthma-related A&E attendance, in-patient admission or out-patient department attendance
b. Acute courses of oral corticosteroids with evidence of a lower respiratory consultation
c. Antibiotics prescribed with evidence of a lower respiratory consultation

B. Overall Asthma Control (Risk Domain and impairment of RDAC)

Controlled asthma is defined here as the absence of the following aspects of asthma risk during the baseline year:

a. Attainment of RDAC, AND
b. Average daily dose of ≤200mcg salbutamol / ≤500mcg terbutaline

Uncontrolled asthma: all others

8.3 GINA guideline definitions low / medium / high daily dose of ICS

Table 1. Low, medium and high daily doses (µg) of inhaled corticosteroids for adults and adoloscents following the GINA guidelines[10]

[11] **Asthma-Related Hospitalisations:** consists of either a definite Asthma Emergency Attendance or a definite Asthma Hospital Admission; OR a generic hospitalisation Read code which has been recorded on the same day as a **Lower Respiratory Consultation**** (see below - excluding where the only lower respiratory code recorded on that day was for a lung function test).
[$] Evidence of a Respiratory Consultation - consists of the following:
a) Any Lower Respiratory Consultation** (see below) and
b) Any additional respiratory examinations, referrals, chest x-rays or events
** Lower Respiratory Consultations - consist of the following:
a) Lower Respiratory read codes (including Asthma and LRTI Read codes)
b) Asthma review codes excl. any monitoring letter codes
c) Lung function and/or asthma monitoring

Age >12 years			
Beclomethasone diproprionate (CFC)[§§§]	200-500	>500-1000	>1000
Beclomethasone diproprionate (HFA)[****]	100-200	>200-400	>400
Budenoside (DPI)[††††]	200-400	>400-800	>800
Ciclesonide (HFA)	80-160	>160-320	>320
Fluticasone proprionate (DPI)	100-250	>250-500	>500
Fluticasone proprionate (HFA)	100-250	>250-500	>500
Mometasone furoate	110-220	>220-440	>440
Triamcinolone acetonide	400-100	>1000-2000	>2000

Table 2. Low, medium and high daily doses (μg) of inhaled corticosteroids for children 5-11 years following the GINA guidelines

Age 5-11 years	Low	Medium	High
Beclomethasone diproprionate (CFC)	100-200	>200-400	>400
Beclomethasone diproprionate (HFA)	50-100	>100-200	>200
Budenoside (DPI)	100-200	>200-400	>400
Budenoside (nebules)	250-500	>500-1000	>1000
Ciclesonide (HFA)	80	>80-160	>160
Fluticasone proprionate (DPI)	100-200	>200-400	>400
Fluticasone proprionate (HFA)	100-200	>200-500	>500
Mometasone furoate	110	≥220-<400	≥400
Triamcinolone acetonide	400-800	>800-1200	>1200

[§§§] CFC: chlorofluorocarbon propellant (included for comparison with older literature)
[****] Hydrofluoralkane propellant
[††††] Dry powder inhaler

8.4 BTS steps of treatment

Table 3. BTS steps for combinations of drugs

BTS Step:	Drug Class Groups:
1	SABA
2	ICS +/- SABA **or** LTRA +/- SABA
3	LABA +/- SABA **or** LABA + THEO[‡‡‡‡] +/- SABA **or** ICS + LABA +/- SABA **or** ICS + LTRA +/- SABA **or** ICS + THEO +/- SABA **or** High dose[§§§§] ICS +/- SABA
4	ICS + LABA + LTRA +/- SABA **or** ICS + LABA + THEO +/- SABA **or** ICS + LABA + LTRA + THEO +/- SABA **or** High dose ICS + LABA +/- SABA **or** High dose ICS + LTRA +/- SABA **or** High dose ICS + THEO +/- SABA
5	High dose ICS + LABA + maintenance oral steroids +/- SABA **or** High dose ICS + LTRA + maintenance oral steroids +/- SABA **or** High dose ICS + THEO + maintenance oral steroids +/- SABA **or** Maintenance oral steroids

[‡‡‡‡] Theophylline
[§§§§] ≥800 micrograms/day BDP equivalent in adults; ≥400 micrograms/day in children aged 5–12 years

8.5 GINA steps of treatment

Table 4. GINA steps for combinations of drugs

GINA Step:	**Drug Class Groups:**
1	SABA **or** LABA +/- SABA(although discouraged without ICS)
2	Low dose (LD) ICS***** +/- SABA **or** LTRA +/- SABA **or** THEO +/- SABA **or** LABA + THEO +/- SABA(although discouraged without ICS) **or**
3	LD ICS + LABA +/- SABA (adults) / Medium dose (MD) ICS + LABA +/- SABA (children) **or** MD ICS +/- SABA LD ICS + LTRA +/- SABA **or** LD ICS + THEO +/- SABA **or** LD ICS + LABA + LTRA +/- SABA **or** LD ICS + LABA + THEO +/- SABA **or** LD ICS + LABA + LTRA + THEO +/- SABA **or**
4	MD /High dose (HD) ICS + LABA +/- SABA (adults) **or** HD ICS + LABA +/- SABA (children)
5	MD/HD ICS + LTRA +/- SABA **or** MD/HD ICS + THEO +/- SABA **or** MD/HD ICS + omalizumab **or** ICS + LABA + Maintenance oral steroids +/- SABA **or** ICS + LTRA + Maintenance oral steroids +/- SABA **or** ICS + THEO + Maintenance oral steroids +/- SABA **or** Maintenance oral steroids

***** For definitions see Appendix 8.3

8.6 Algorithm for definition of probably acute versus probable chronic oral corticosteroids prescriptions ions