REG Study Protocol

Long Title: The reliability and utility of blood eosinophils as a marker of disease burden, healthcare resource utilisation and response to treatment in chronic obstructive pulmonary disease

Short Title: Blood eosinophil count and COPD

Research Protocol developed by The Respiratory Effectiveness Group
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ABBREVIATIONS & DEFINITIONS

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<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>ICS</td>
<td>Inhaled glucocorticosteroid</td>
</tr>
<tr>
<td>LABA</td>
<td>Long-acting bronchodilator</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>REG</td>
<td>Respiratory Effectiveness Group</td>
</tr>
<tr>
<td>RiRL</td>
<td>Research in Real Life Ltd</td>
</tr>
<tr>
<td>SABA</td>
<td>Short-acting bronchodilator</td>
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</table>

BACKGROUND & RATIONALE

COPD is characterized by irreversible airflow obstruction. The physiological abnormalities observed in COPD are due to a combination of emphysema, chronic bronchitis and obliteration of the small airways in association with airway inflammation. The predominant cells involved in this inflammatory response are CD8+ lymphocytes, neutrophils, and macrophages. Although eosinophilic airway inflammation is usually considered a feature of asthma, it has been demonstrated in large and small airway tissue samples taken from patients with COPD and in 20%–40% of induced sputum samples from patients with stable COPD [1-6].

The development of sputum induction as a non-invasive test of airway inflammation has enabled clinicians to study the phenotype of airway inflammation in patients with airway disease. In this way, a normal sputum eosinophil count has been assessed as <1.1% and counts in excess of 3% have been shown to be associated with a good response to oral [5, 7] and inhaled [3] corticosteroids in COPD, confirming data previously obtained with bronchoalveolar lavage [8].

Utility of blood eosinophils as a biomarker in asthma

Recent work in a severe (NHANES) asthma population (n~10,000) suggests blood eosinophils may be more predictive of sudden severe exacerbations requiring emergency room (ER) assessment than fractional exhaled nitric oxide [9]. Moreover, the study suggests blood eosinophils can be used to identify a group of at-risk asthma patients, independent of symptom control.

Data from a recent observational study conducted by Research in Real Life Ltd and led by Professor David Price (lead investigator for this study) suggest that patients with blood eosinophil counts in excess of 400/µL are more intensively managed (higher management step and same or higher mean daily ICS dose), have more exacerbations (1.4-fold more) and have reduced odds of achieving asthma control (1.3-fold reduction) [10]. The data suggest a continuous, linear relationship between eosinophil count and asthma control (i.e. that the higher a patient’s blood eosinophil count, the lower their odds of achieving asthma control).

Utility of blood eosinophils as a biomarker in COPD
Bronchial biopsy have shown that, compared to levels in stable COPD controls, airway eosinophils increase significantly (a 30-fold increase) during COPD exacerbations [11, 12].

A recent study investigated the potential utility of blood eosinophils to direct corticosteroid therapy during COPD exacerbations [13]. Patients experiencing COPD exacerbations (n=166) were randomized to either a usual care arm (defined as 2 weeks of prednisolone) or to a biomarker-directed, double-blind corticosteroid arm (where prednisolone or placebo was administered according to the blood eosinophil count biomarker). Eosinophil-guided treatment was found to be non-inferior to usual care in terms of improvement in chronic respiratory questionnaire (CRQ). While they acknowledged larger studies are still required, the authors concluded that peripheral blood eosinophil count is a promising biomarker to direct oral corticosteroid therapy during COPD exacerbations [13].

In terms of its utility as a predictor of future risk, eosinopenia is the E in the DECAF Score which was developed by a group looking at predictors of mortality (in-hospital death) in patients hospitalised with COPD exacerbations. The five strongest predictors of death were: (i) extended Medical Research Council (MRC) Dyspnoea Score, (ii) Eosinopenia, (iii) Consolidation, (iv) Acidaemia, and (v) atrial Fibrillation (DECAF). During internal bootstrap validation, the DECAF Score showed excellent discrimination for mortality and performed more strongly than other clinical prediction tools. The authors concluded that the DECAF Score is a simple yet effective predictor of mortality in patients hospitalised with an exacerbation of COPD and has the potential to help clinicians predict prognosis more accurately [14].

Thus blood eosinophil count could be a useful marker to identify future risk in COPD patient subgroups. Eosinopenia appears to be an important predictor of mortality in patients experiencing acute COPD exacerbations, but in patients with stable COPD, it is eosinophilia that is thought to be the more important marker of modifiable future risk. Further work is required to explore the potential utility of blood eosinophil level as a predictor of future risk in stable COPD and/or as a predictor of response to risk-reducing therapy.

The proposed study

The primary aim of the proposed study is to explore the relationship between blood eosinophil count and future exacerbation risk in COPD and effect of preventative COPD therapy on eosinophil level. Additional analysis will also aim to investigate the stability of the phenotype, defined by change in eosinophils over time and in response to treatment.

Exploratory investigations will also seek to characterise features of COPD patients with eosinophilia in terms of their COPD stage and categorisation, comorbid conditions and other clinical characteristics (respiratory symptoms, past history of exacerbations, risk factors).

AIM & OBJECTIVE

This study will be the first in a series of REG-funded studies designed to explore the relationship between blood eosinophil count, COPD disease status, COPD exacerbations and to explore its value and utility as a measureable marker of future risk in COPD.
In particular, this study aims to:

- Establish the relationship between blood eosinophil count and:
  - Future COPD exacerbations.
  - Response to preventative COPD therapy; and
- Investigate the stability of the phenotype, defined by change in eosinophils over time and in response to treatment.

### STUDY DESIGN, DATASET AND METHODOLOGY

**Study Design**

This will be a prospectively planned (and registered) retrospective observational study using data from the Optimum Patient Care Research Database (OPCRD).

The study will consist of:

- An index date, when patients receive their last valid (with a numeric value recorded at least one year prior to the last date of the data extraction) blood eosinophil record
- At least one-year baseline period immediately before the index date for baseline patient characterisation
- A one-year outcome period immediately after the index date for outcome evaluation.

**Data source**

The OPCRD comprises data extracted through the Optimum Patient Care (OPC) Clinical Service Evaluation. The clinical evaluation involves a combined review of (anonymised) electronic medical records (EMRs) and patients’ responses to disease-specific questionnaires and characterizes patients in terms of their demography, disease control and exacerbation history. The review process produces patient-level reports that makes guideline-based recommendations for possible management changes to optimise control at the lowest possible therapeutic dose and reduce potential future exacerbation risk.

At the time of writing, OPCRD contains anonymised, research-quality data for approximately 100,000 patients with chronic obstructive pulmonary disease [COPD] (and 300,000 patients with asthma) collected from more than 300 practices across the UK that subscribe to the OPC Clinical Service Evaluation (see Appendix 1 for OPCRD Data Dictionary).

**Study Period**

The study period will run for a continuous ≥2-year period: at least one baseline year before the index date (at which point patients’ last valid blood eosinophil reading was recorded) and one outcome year after the index date.

**Study Phases & Analysis**

The study will consist of a number of sequential elements:

- **Phase 1**: Association between blood eosinophilia and outcomes:
 Phase 1a: Baseline characterisation phase vs controls

The study population and a control population will be characterised over a one-year baseline period in terms of demography, clinical characteristics and healthcare resource utilisation (see page 13 for full list of descriptive variables) and compared to identify potential differences between patients whose blood eosinophil level is recorded, and those in whom it is not measured.

A control population will have no blood eosinophil record, but will meet all other inclusion criteria of the study population except. The mean year of index date of the study population will be used to inform the appropriate 1-year period for control extraction and cross-sectional characterisation.

- Will determine the relationship between eosinophil counts and future exacerbations (0, 1, 2–3, ≥4; see page 10 for outcome definitions). Relationship between eosinophil count and future exacerbations will be explored for the full study population and for subgroups of particular clinical interest (see “Subgroups” section on page 9 of this protocol).

Eosinophil count will be evaluated as both a continuous and a dichotomous variable. The appropriate threshold for “high eosinophil count” will be informed by the distribution of eosinophil counts in the study population and by prior work in this area:

  - The threshold for high vs normal eosinophil count in the aforementioned asthma study conducted using the OPCRD was set at (≤400/µL vs >400/µL, respectively)
  - Previous studies in suggest a range of median and thresholds levels for blood eosinophils:
    - The limit of normal of blood eosinophilia in healthy individuals (no asthma or airflow obstruction) appeared to be 270/µL [15].
    - The optimal cut-off point (on the ROC curve) of blood eosinophilia in patients with asthma as a predictor of the presence of airway eosinophilia was 220/µL [16].
    - In the AZISAST study, median blood eosinophilia in patients with severe asthma found to be 200/µL [17].
    - A study of 19 asthma patients and 20 controls designed to compare the different biomarkers found median blood eosinophils among asthma patients to be significantly higher than for non-asthma controls (350.0 µL [144.0–1520.0µL] vs 155.0µL [34.0 to 426.0µL]; p = 0.003) [18].

Drawing on these data the threshold for COPD is expected to be between 200–350/µL. However, the optimum threshold for the planned dichotomous analysis will be determined by the eosinophil distribution within the study population.
**Phase 2 – “Validation phase”:** Will investigate the stability of the phenotype, defined by change in eosinophils over time and in response to treatment.

In the **subgroup of patients with sequential blood eosinophil readings** establish that eosinophil count is:

- Stable and repeatable (using valid steady state readings measured outside a 4-week window around an exacerbation)
- Responsive to change. Specifically, does blood eosinophil count change:
  - In response to COPD treatment (ICS, LABA, LAMA) (a comparison of the last steady state blood eosinophil level recorded before a change in therapy, and the first valid steady state measurement after the change in therapy)
  - During COPD exacerbations (a comparison of blood eosinophil records within vs outside a 4-week window around an exacerbation)

**Exploratory phases:**

1 Note: many patients in the UK will have full blood counts performed as part of disease monitoring for their comorbid conditions (e.g. ischemic heart disease, diabetes, etc), thus patients with successive blood eosinophil readings may not be a more severe group, but their markers of disease severity will be characterized to allow comparison of the population to the full study population.
- **Exploratory 1**: Explore the relationship between:
  - Childhood asthma and eosinophilia
  - Atopy and eosinophilia

- **Exploratory 2**: Bafadhel et al’s study suggests steady state eosinophilia predicts eosinophilic exacerbations (not bacterial or viral). It is also suggested that eosinophilic exacerbations may be more severe (resulting in more frequently hospitalization) and require oral steroid treatment [13].

  To explore the “appropriateness” of exacerbation management in patients with raised eosinophils, the association between baseline exacerbation treatment (oral steroid treatment, antibiotics, or oral steroids+antibiotics) and future exacerbation rates will be explored as a proxy for “exacerbation treatment failure” in patients with raised compared with normal eosinophil levels.

- **Exploratory 3**: For patients with multiple “valid” blood eosinophil reading, characterise the variation in reading and explore which of the following is the most predictive of future exacerbation risk: lowest (possible negative association); mean/median (average level over time); highest.

- **Exploratory 4**: Explore the relationship between low blood eosinophil level and sepsis (using incidence of antibiotic-treated infections as a proxy).

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**STUDY POPULATION**

**Inclusion criteria**

Owing to incomplete lung function data within primary care datasets, and in order to maximize the size and “real-life” nature of the study population, all patients with a physician diagnosis of COPD rather than a strict, spirometrically-defined COPD population will be eligible for the study. A subgroup analysis will be conducted in those patients with spirometry-defined COPD. Where data are available, results will also be stratified by GOLD stage and category (i.e. ABCD category).

To be eligible for inclusion in the study, patients must meeting the following inclusion criteria:

- Have ≥1 recorded blood eosinophil count
- ≥2 years of continuous medical records
  - ≥1 baseline year immediately prior to the first recorded blood eosinophil count
  - ≥1 outcome years immediately following the first recorded blood eosinophil count
- Aged ≥40 years
- Have physician-diagnosed COPD i.e. Read coded diagnosis.

**Exclusion criteria**

To minimize the risk of possible confounding of results, the following patients will be excluded from the study population:

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²Age will be the patient’s age at the time of their first recorded blood eosinophil count
• Patients with any physician-diagnosed (i.e. Read Code diagnosed) respiratory condition other than COPD or asthma

Eligibility criteria

The National Institute for Health and Clinical Excellence (NICE) in England and Wales recommends full blood counts be measured as part COPD diagnosis [20]. Moreover, the Quality Outcomes Framework in the UK incentivises measurement of full blood counts for a number of chronic conditions.[21] Thus the presence of a blood eosinophil record may not be a marker of more severe COPD in the study population, or associated with a worsening of the patients COPD status.

Steady state blood eosinophil count and elevated exacerbation counts will be differentiated so that the association between steady state count (see below) and exacerbation rates can be evaluated as well as change in steady state count in response to (i) exacerbations (ii) treatment change.

The following “valid” blood eosinophil count defintions will be used:

• **Steady State**: a blood eosinophil count will be considered a valid steady state count if it is recorded at least 4 weeks prior to, or after, a COPD exacerbation
• **Exacerbation**: a blood eosinophil count will be considered a valid exacerbation count if it is recorded within a 4-week window around a COPD exacerbation

Full blood count (and change in FBC within a 4-week window around a COPD exacerbation) will be used as a marker to validate this approach.

Sub-groups

To minimize concerns over inclusion of patients misdiagnosed with COPD (e.g. those with asthma) and potential confounding of the results, the analysis will be repeated in the subgroup of patients who meet the additional inclusion criteria of:

**Active COPD therapy**: defined as multiple (i.e. ≥2) prescriptions for any respiratory drug during both the baseline and outcome years. The findings of the active therapy subgroup will be compared with those of the full study population to assess consistency (or to note divergence) of signal.

**Spirometry records**: having spirometry records consistent with the presence of airway obstruction. The findings of the spirometry-defined COPD subgroup will be compared with those of the full study population to assess consistency (or to note divergence) of signal.

**Comorbid asthma**: findings for the subgroup of patients with a comorbid asthma diagnosis will be compared with those of the full population and with the subgroup of patients without a comorbid asthma diagnosis to assess consistency (or to note divergence) of signal.

**Comorbid rhinitis**: findings for the subgroup of patients with a comorbid rhinitis (allergic and non allergic) diagnosis will be compared with those of the full population and with the subgroup of patients without a comorbid rhinitis diagnosis to assess consistency (or to note divergence) of signal.

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3 For the purposes of this study, bronchiectasis will be excluded
No history of atopy: findings for the subgroup of patients with no history or evidence of atopy will be compared with the full population to assess consistency (or to note divergence) of signal.

Smoking status: findings for the subgroup of patients who have current, ex- and non-smoking statuses will be reported separately and compared to assess variation in signal (in acknowledgement of past work reporting increased risk to respiratory symptoms in hyperresponsive current smokers when eosinophilia [19])

Comorbidities: findings for the subgroups of patients who have one, multiple (≥2) and no comorbid chronic disease diagnoses will be compared to assess the potential effect of other chronic disease on eosinophil level and its predictive quality.

Gender: findings for the subgroups female patients will be compared to those for the full population and for male patients to assess consistency (or to note divergence) of signal in different gender groups.

Possible age subgroups analyses will be considered once the distribution of age within the population has been established to determine whether the number of patients in clinically relevant subgroups are sufficient to warrant subgroup analyses.

**COMPARISON GROUPS**

Patients will be categorized in terms of their blood eosinophil levels. Levels will be captured using actual recorded numerical blood-eosinophil counts, split as normal and raised (“raised” will be defined having reviewed the distribution of eosinophil counts across the study population, but is expected to be in the region of >200 µL, >220 /µL or >300 /µL). (see Appendix 2a for Eosinophil Code Lists).

**OUTCOMES**

*Phase 1: Evaluating the relationship between eosinophil count and future exacerbations*

Exacerbation number and exacerbation rate ratios will be evaluated for patients with raised blood eosinophil count and compared with those of patients without a high blood eosinophil count recorded. A proxy marker of adherence will also be evaluated to investigate the relationship between elevated eosinophil level, exacerbation risk and treatment adherence.

Differences between the comparator groups that may be potential confounders (e.g. demographic features, GOLD status and markers of COPD disease status) will be identified during the baseline characterisation period, and used in the statistical modelling.

Exacerbations* will be defined as:

1. Unscheduled hospital admission or A&E attendance for either COPD or lower respiratory events

*Two exacerbations recorded within a 2-week window of each other will be treated as one exacerbation*
2. An acute course of oral steroids prescribed with evidence of respiratory review within the last 2 weeks; OR
3. Antibiotics prescribed with evidence of respiratory review within the last 2 weeks.

In the UK, patients on a self-management plan often receive “home (or rescue) packs” of steroids and antibiotics, which would be prescribed during a routine review, there could be a mismatch between prescription date and exacerbation date in such patients. In recognition of this, a sensitivity analysis will be conducted using antibiotic and oral steroid prescriptions with acute lower respiratory code.

**Adherence:** assessed as medication possession ratio (MPR, defined as: [total days of therapy covered within the outcome year/365]x100) will be evaluated as an outcome to explore whether high eosinophil levels are the result of poor adherence.

**Phase 2: Investigate the stability of the phenotype, defined by change in eosinophils over time and in response to treatment**

The index date will be the date of last valid eosinophil reading. Prior eosinophil readings over the baseline period will be compared to assess:

(a) **Stability and repeatability of eosinophil levels:** changes between successive valid steady state eosinophil records.

(b) **Effect of changes in therapy on eosinophil count:** where a change in therapy is initiation of new therapy (ICS, LABA or LAMA) or a step-up (≥50% dose increase) of existing therapy (ICS, LABA or LAMA). The last valid steady state record prior to treatment change and the first valid steady state record following treatment change will be assessed.

(c) **In response to a COPD exacerbation:** Change in blood eosinophil count before–during and during-after COPD exacerbations will be evaluated by comparing steady state and exacerbation blood eosinophil counts, i.e. those recorded within and outside a 4-week window around an exacerbation.

**Exploratory analyses**

**Phase 3: Exploring the relationship between patient characteristics and raise blood eosinophils**

GOLD status and ABCD classification (where evaluable) and prevalence of childhood asthma and evidence of atopy will be evaluated for patients with / without recorded eosinophilia (at any stage) during the study period:

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5 Evidence of a Respiratory Review - consists of the following:
- Any Lower Respiratory Consultation (see above) and any
- Additional respiratory examinations, referrals, chest x-rays, or events.

6 Comparison of last eosinophil reading prior to a therapy change and first reading following the therapy change

7 Comparison of last eosinophil reading prior to an exacerbation, (where available) at the time of the exacerbation and subsequent readings
(a) GOLD status

(ai) Classification of severity of airflow limitation in COPD (based on post-bronchodilator FEV1) [22]

In patients with FEV1/FVC<0.70:

GOLD 1: Mild  FEV1≥80% predicted
GOLD 2: Moderate  50%≤FEV1<80% predicted
GOLD 3: Severe  30%≤FEV1<50% predicted
GOLD 4: Very Severe  FEV1<30% predicted

(aii) Combined (symptom, airflow limitation, exacerbation) assessment of COPD (A, B, C, D classification) [22]

<table>
<thead>
<tr>
<th>Patient</th>
<th>Characteristic</th>
<th>Spirometric Classification</th>
<th>Exacerbations per year</th>
<th>mMRC</th>
<th>CAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low risk</td>
<td>GOLD 1–2</td>
<td>≤1</td>
<td>0–1</td>
<td>&lt;10</td>
</tr>
<tr>
<td>B</td>
<td>Low Risk</td>
<td>GOLD 1–2</td>
<td>≤1</td>
<td>≥2</td>
<td>≥10</td>
</tr>
<tr>
<td>C</td>
<td>High Risk</td>
<td>GOLD 3–4</td>
<td>≥2</td>
<td>0–1</td>
<td>&lt;10</td>
</tr>
<tr>
<td>D</td>
<td>High Risk</td>
<td>GOLD 3–4</td>
<td>≥2</td>
<td>≥2</td>
<td>≥10</td>
</tr>
</tbody>
</table>

(b) Childhood asthma

Childhood asthma will be defined and assessed in two ways:

(i) Presence of a diagnostic code for asthma (see list below) between 5–18* years
(ii) Presence of a diagnostic code or ≥2 prescriptions for asthma therapy between 5–18* years.

* Infant diagnoses (recorded in years 0–5 years) will be excluded due to potential overestimation of childhood asthma through confounding by recurrent viral wheeze being mis-diagnosed as asthma.

(See Appendix 2b for code lists)

(c) Evidence of atopy

Atopy will be evaluated using proxy measures, specifically presence of Read codes or indicative prescriptions as summarised below:

- **Allergic rhinitis** (read code ever)\(^8\)
- **Animal allergies** (read code ever)
- **Chronic rhinosinusitis** (read code ever)

\(^8\) Except cases of non-atopic polyposis
• **Hay Fever** (read code ever)
• **Other rhinitis-related Read codes** (read code ever)
• **Seasonal rhinitis**: Patients with a hay fever code ever recorded, receiving at least one prescription during the study period but only in hay-fever season.
• **Eczema** (read code ever)
• Repeat (≥2) topical nasal steroid prescriptions
• Repeat (≥2) topical tacrolimus prescriptions
• Repeat (≥2) topical pimecrolimus prescriptions
• Objectivity measured / recorded atopy (e.g.). Phadiatop.

See Appendix 2c for code lists.

**Objective 4: Exploring the relationship between very low blood eosinophil level and sepsis**

Report the number of antibiotic prescriptions (as a proxy for potential sepsis) against different blood eosinophil categories: eosinophilia, normal, low, eosinopenia.

### DATA AND STATISTICAL ANALYSIS

Summary statistics will be calculated for the following variables by blood-eosinophil count status, raised and normal, and compared:

- Demographics examined at (or closest to) the relevant index date (including age, gender, BMI, smoking status);
- Co-morbidities examined regardless of when they occurred relative to the index date (including eczema; rhinitis diagnosis – allergic and non-allergic; cardiovascular disease; gastrooesophageal reflux disease; depression and anxiety) and CCI score examined in the year before the index date and in the outcome period;
- Number of exacerbations in the year before the index date and in one- and two-year periods immediately after index date;

For variables measured on the interval or ratio scale, summary statistics produced will be:

- Sample size (n)
- Percentage non missing
- Mean
- Variance/standard deviation
- Range (minimum- maximum)
- Median
- Inter-quantile range (25th and 75th percentile)

For categorical variable the summary statistics will include:

- Sample size (n)
- Range (if applicable)
- Count and percentage by category (distribution)

Outcomes will be compared using a Mann Whitney U test/Chi squared Test (for variables measured on the interval or ratio scale/ categorical variables respectively.)
Phase 1: will assess whether a raised eosinophil count is predictive of future COPD exacerbations. The expected number of exacerbations will be modelled with a Poisson regression model. Significant predictors of raised eosinophil count will be included in the model, as well as other potential baseline confounders.

Phase 2: will evaluate the presence and nature of change between successive blood eosinophil counts and categorised changes as:

1. Decrease: if eosinophil count reduces by >XµL
2. Stable/no change: if eosinophil count alters by a clinically insignificant amount, i.e. change ≤XµL
3. Increase: if eosinophil count increases by >XµL

Where “X” is a non-zero amount determined by the distribution of eosinophil change within the study population and will agreed by the Study’s Steering Committee before Phase 2 of the analysis commences.

A multinomial logistic regression will be used to compare the probability of decreasing/increasing the eosinophil count as function of therapy and exacerbations.

Phase 3: will evaluate the probability of (i) having childhood asthma and (ii) GOLD stage as predictors of a raised eosinophil count. Logistic regression modeling will be used.

Phase 4: will explore treatment failure in patients with raised vs normal eosinophil counts. A logistic regression modeling will be used to compare the probability of increasing exacerbation rate as function of eosinophil count and exacerbations treatment.

Phase 5: will assess the number of infections (as a proxy for possibly sepsis) in patients with low blood eosinophil counts. The appropriate threshold for “low eosinophil count” will be determined by the distribution of eosinophil counts across the study population. The suspected number of events will be modelled with a Poisson regression model. Significant predictors of raised eosinophil count will be included in the model, as well as other potential baseline confounders.

Statistically significant results will be defined as p<0.05 and trends as 0.05≤p<0.10.

STEERING COMMITTEE INVOLVEMENT

The study will be overseen by an independent steering committee comprising members of the Respiratory Effectiveness Group (REG). REG is a not-for-profit organization that brings together respiratory experts from around the world with the shared goal of raising the quality and profile of real-life research (both observational studies and pragmatic trials) through a series of research, communication, standards-related and advocacy activities.

REG is funded by multiple partners, but its activities are set, agreed and conducted by the REG collaborators (directed by the management steering committee) and, where appropriate, independent contract research organisations.

This protocol has been informed by the views and suggestions of the steering group; the data from the study, subsequent analyses and its dissemination will be approved by the
steering group. The composition of the study steering group is detailed in the **Study Team** section of this protocol.

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### PATIENT INVOLVEMENT

At the time of writing, there are no patient experts or advocates involved in the planning and/or review of this study.

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### LIMITATIONS OF STUDY DESIGN / ANALYSIS

As with all database studies a number of limitations existed such as incomplete data and the need to use proxy measures where explicit data are not available. In routine practice records there will be no (or sparse) data available on sputum cultures or C-reactive protein (CRP) and incomplete lung function data.

The data from observational studies should be viewed as one element of the overall evidence base and considered in combination with data from other study designs, e.g. pragmatic trials and randomized controlled trials (RCTs).

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### DATA DISSEMINATION PLANS

REG is committed to registering (typically in the ClinicalTrials.Gov or ENCePP e-registries) and publishing all of the studies it undertakes and to ensure transparency of its activities so that REG-funded research can be used to inform the research and lay community.

At least one abstract from the study will be submitted to a key international respiratory congress (e.g. the European Respiratory Society, American Thoracic Society or similar) and at least one manuscript will be developed and submitted for to a peer review respiratory journal to disseminate the primary elements of the planned analysis.

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### STUDY TEAM

The study team is an international group of expert respiratory clinicians and researchers working collaboratively on behalf of the Respiratory Effectiveness Group. Data analysis and statistical support will be contracted from Research in Real Life Limited.

**Lead investigator**

**David Price**: Primary Care Respiratory Society UK, Professor of Primary Care Respiratory Medicine, Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, UK and Founding Member of the Respiratory Effectiveness Group, Cambridge, UK

**Respiratory Effectiveness Steering Committee**

**Antonio Anzueto**: Pulmonary Critical Care Center, San Antonio, TX, USA

**Alvar Augusti**: Hospital Clinic, IDIBAPS, Universitat de Barcelona and CIBER Enfermedades Respiratorias, FISIB, Mallorca, Spain

**Mona Bafadhel**: Glenfield Hospital, Leicester, UK
Data analysis
Anna Rigazio: Data Analyst and Statistician, Research in Real Life Ltd, Cambridge, UK

ETHICS

The OPCRD has been approved by Trent Multi Centre Research Ethics Committee for clinical research use, and this study protocol will be submitted to OPCRD’s Anonymised Data Ethics Protocols and Transparency (ADEPT) Committee for approval to sanction the use of the OPCRD for the purposes of the proposed study.

REFERENCES


10. Data on file at the time of writing


20. Chronic obstructive pulmonary disease, NICE Clinical Guideline (June 2010)


22. Global Initiative for Chronic Obstructive Lung Disease. Pocket Guide to COPD
APPENDICES

Appendix 1: OPCRD data dictionary

1. Patient

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

<table>
<thead>
<tr>
<th>Field Name</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient_ID</td>
<td>Anonymised patient identifier</td>
</tr>
<tr>
<td>Practice_ID</td>
<td>Unique practice identifier.</td>
</tr>
<tr>
<td>Year_Of_Birth</td>
<td>Patient year of birth in format YYYY</td>
</tr>
<tr>
<td>Gender</td>
<td>Patient gender</td>
</tr>
<tr>
<td>Status</td>
<td>Patient registration status - (R) – Registered, (L) – Left, (D) - Death</td>
</tr>
<tr>
<td>Joined_Date</td>
<td>Date joined practice or date first registered on database</td>
</tr>
<tr>
<td>Leaving_Date</td>
<td>Date left practice or date first registered on database</td>
</tr>
<tr>
<td>Leaving_Reason</td>
<td>Reason for leaving practice</td>
</tr>
<tr>
<td>Post_Code</td>
<td>“Out” part of patient postcode and first character of “in” part of patient postcode</td>
</tr>
</tbody>
</table>

2. Clinical

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

<table>
<thead>
<tr>
<th>Field Name</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient_ID</td>
<td>Anonymised patient identifier</td>
</tr>
<tr>
<td>Event_Date</td>
<td>Date of event</td>
</tr>
<tr>
<td>Read_Code</td>
<td>Five byte read code for event including terminal code if available</td>
</tr>
<tr>
<td>Read_Term</td>
<td>Rubric associated with read_code</td>
</tr>
<tr>
<td>Numeric_1</td>
<td>First numeric value if stored</td>
</tr>
<tr>
<td>Numeric_2</td>
<td>Second numeric value if stored</td>
</tr>
<tr>
<td>Text</td>
<td>First 50 characters of any text associated with entry</td>
</tr>
</tbody>
</table>

3. Referral

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

<table>
<thead>
<tr>
<th>Field Name</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient_ID</td>
<td>Anonymised patient identifier</td>
</tr>
<tr>
<td>Event_Date</td>
<td>Date of event in format dd/mm/yyyy</td>
</tr>
</tbody>
</table>
4. Therapy

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

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

5. Practice

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

<table>
<thead>
<tr>
<th>Field Name</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>PracticeID</td>
<td>Unique OPC practice id</td>
</tr>
<tr>
<td>Practice_NHS</td>
<td>Unique NHS practice identifier.</td>
</tr>
<tr>
<td>Practice_Name</td>
<td>Name of practice</td>
</tr>
<tr>
<td>Practice_Address1</td>
<td>Address line 1</td>
</tr>
<tr>
<td>Practice_Address2</td>
<td>Address line 2</td>
</tr>
<tr>
<td>Practice_Address3</td>
<td>Address line 3</td>
</tr>
<tr>
<td>Practice_Address4</td>
<td>Address line 4</td>
</tr>
<tr>
<td>Practice_Postcode</td>
<td>Post Code</td>
</tr>
<tr>
<td>Practice_list_size</td>
<td>Total practice list size</td>
</tr>
<tr>
<td>Last_Extract_Date</td>
<td>Date when practice last did an extract</td>
</tr>
</tbody>
</table>

6. COPD Questionnaire Data Collection
The **COPD Questionnaire Data Collection** file contains the data collected from the questionnaires received from patients participating in the OPC COPD Review Service. The file provides the original response as well as calculated values derived from the patient responses to the questions.

Questions currently being surveyed are the following:

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>I never cough / I cough all the time.</td>
<td>An answer from 1 to 6 will indicate which statement best describes the impact COPD is having on their wellbeing and daily life.</td>
</tr>
<tr>
<td>I have no phlegm (mucus) on my chest at all / My chest is completely full of mucus.</td>
<td>An answer from 1 to 6 will indicate which statement best describes the impact COPD is having on their wellbeing and daily life.</td>
</tr>
<tr>
<td>My chest does not feel tight at all / My chest feels very tight.</td>
<td>An answer from 1 to 6 will indicate which statement best describes the impact COPD is having on their wellbeing and daily life.</td>
</tr>
<tr>
<td>When I walk up a hill or one flight of stairs I am not breathless / When I walk up a hill or one flight of stairs I am very breathless.</td>
<td>An answer from 1 to 6 will indicate which statement best describes the impact COPD is having on their wellbeing and daily life.</td>
</tr>
<tr>
<td>I am not limited doing any activities at home / I am very limited doing activities at home.</td>
<td>An answer from 1 to 6 will indicate which statement best describes the impact COPD is having on their wellbeing and daily life.</td>
</tr>
<tr>
<td>I am confident leaving my home despite my lung condition / I am not at all confident leaving my home because of my lung condition.</td>
<td>An answer from 1 to 6 will indicate which statement best describes the impact COPD is having on their wellbeing and daily life.</td>
</tr>
<tr>
<td>I sleep soundly / I don't sleep soundly because of my lung condition.</td>
<td>An answer from 1 to 6 will indicate which statement best describes the impact COPD is having on their wellbeing and daily life.</td>
</tr>
<tr>
<td>I have lots of energy / I have no energy at all.</td>
<td>An answer from 1 to 6 will indicate which statement best describes the impact COPD is having on their wellbeing and daily life.</td>
</tr>
<tr>
<td>I need to take my inhaler(s) regularly.</td>
<td>Strongly Disagree / Disagree / Not sure / Agree / Strongly Agree</td>
</tr>
<tr>
<td>I find inhaler(s) difficult to use.</td>
<td>Strongly Disagree / Disagree / Not sure / Agree / Strongly Agree</td>
</tr>
<tr>
<td>I worry about the side effects of my COPD inhaler(s).</td>
<td>Strongly Disagree / Disagree / Not sure / Agree / Strongly Agree</td>
</tr>
<tr>
<td>I have enough information about my inhaler(s).</td>
<td>Strongly Disagree / Disagree / Not sure / Agree / Strongly Agree</td>
</tr>
<tr>
<td>I would prefer to take my regular COPD medications in a once-a-day dose.</td>
<td>Strongly Disagree / Disagree / Not sure / Agree / Strongly Agree</td>
</tr>
<tr>
<td>Thinking about how often you take your regular COPD treatment during the day:</td>
<td>1 = I always take it exactly at the time prescribed. 2 = I occasionally miss the odd dose. 3 = I often miss or forget to take doses. 4 = I take all once a day - it's easier. 5 = I never take it.</td>
</tr>
<tr>
<td>Which statement best describes how you take your regular COPD treatment.</td>
<td>1 = I take it every day. 2 = I take some days but others I do not. 3 = I used to take but now I do not. 4 = I take only when I have symptoms. 5 = I never take it.</td>
</tr>
<tr>
<td>Question</td>
<td>Response</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Have you seen a specialist respiratory doctor or nurse outside the practice?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Thinking about breathlessness, which statement best describes you?</td>
<td>1 = Not troubled by breathlessness. 2 = Short of breath when hurrying or walking up a slight hill. 3 = Slower in walking than other of the same on the level because of breathlessness, or have to stop for breath when walking at your own pace. 4 = Stopping for breath after about 100m or after a few minutes on the level. 5 = Too breathless to leave the house, or breathless when dressing / undressing.</td>
</tr>
<tr>
<td>Which best describes you?</td>
<td>1 = Never smoked, 2 = Current Smoker, 3 = Ex-smoker</td>
</tr>
<tr>
<td>How many cigarettes do/did you smoke per day?</td>
<td>1-5; 6-10; 11-15; 16-20; 21-30; 31-40; 41-50; &gt;50</td>
</tr>
<tr>
<td>How many years have you smoked/did you smoke?</td>
<td>1-5; 6-10; 11-15; 16-20; 21-30; 31-40; 41-50; &gt;50</td>
</tr>
<tr>
<td>In the past year, have you had your Inhaler technique checked?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>In the past year, how many times have you been admitted to hospital with breathing problems?</td>
<td>0, 1, 2, 3, 4, 5 or more</td>
</tr>
<tr>
<td>In the past year, how many times have you had a worsening of your chest symptoms requiring a course of steroid tablets and/or antibiotics?</td>
<td>0, 1, 2, 3, 4, 5 or more</td>
</tr>
<tr>
<td>Do you have any of these symptoms: itchy, runny, blocked nose or sneezing when you don't have a cold?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Thinking about exercise, how much time do you spend doing exercise/activity (eg walking) each day?</td>
<td>None / 15mins / 30mins / 45mins / 1 hr / 2 hrs / 3 hrs or more</td>
</tr>
<tr>
<td>In the future, would you be willing to participate in further questionnaire based research?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Do you have home oxygen therapy (either cylinders, liquid oxygen or a concentrator?)</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>
### APPENDIX 2: READ CODE LISTS FOR THE ANALYSIS

#### 2a. List of eosinophil diagnostic codes

New list of codes for Eosinophil count

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y108z</td>
<td>Acute eosinophilic pneumonia</td>
</tr>
<tr>
<td>D403300</td>
<td>Allergic eosinophilia</td>
</tr>
<tr>
<td>D4033</td>
<td>Allergic eosinophilia</td>
</tr>
<tr>
<td>D403</td>
<td>Allergic eosinophilia</td>
</tr>
<tr>
<td>Y20fu</td>
<td>Allergic eosinophilia</td>
</tr>
<tr>
<td>X102G</td>
<td>Asthmatic pulm eosinophilia</td>
</tr>
<tr>
<td>Y1094</td>
<td>Asthmatic pulm eosinophilia</td>
</tr>
<tr>
<td>Y1096</td>
<td>Chronic eosinophilic pneumonia</td>
</tr>
<tr>
<td>Y1098</td>
<td>Chronic pulmonary eosinophilia</td>
</tr>
<tr>
<td>Y1097</td>
<td>Crypt eosinophilic pneumonia</td>
</tr>
<tr>
<td>X102H</td>
<td>Cryptogenic pulm eosinophilia</td>
</tr>
<tr>
<td>Y1095</td>
<td>Cryptogenic pulm eosinophilia</td>
</tr>
<tr>
<td>42K2.00</td>
<td>Eosinopenia</td>
</tr>
<tr>
<td>42K2</td>
<td>Eosinopenia</td>
</tr>
<tr>
<td>42K</td>
<td>Eosinopenia</td>
</tr>
<tr>
<td>Y7FAi</td>
<td>Eosinopenia</td>
</tr>
<tr>
<td>X80VM</td>
<td>Eosinopenia</td>
</tr>
<tr>
<td>Y80lD</td>
<td>Eosinopenia</td>
</tr>
<tr>
<td>42K_.00</td>
<td>Eosinophil count</td>
</tr>
<tr>
<td>42K.</td>
<td>Eosinophil count</td>
</tr>
<tr>
<td>42K</td>
<td>Eosinophil count</td>
</tr>
<tr>
<td>Y7FAh</td>
<td>Eosinophil count - observation</td>
</tr>
<tr>
<td>YakcK</td>
<td>Eosinophil count - observation</td>
</tr>
<tr>
<td>42K1.00</td>
<td>Eosinophil count normal</td>
</tr>
<tr>
<td>42K1</td>
<td>Eosinophil count normal</td>
</tr>
<tr>
<td>42K1</td>
<td>Eosinophil count normal</td>
</tr>
<tr>
<td>Y7FAi</td>
<td>Eosinophil count normal</td>
</tr>
<tr>
<td>42KZ.00</td>
<td>Eosinophil count NOS</td>
</tr>
<tr>
<td>42KZ</td>
<td>Eosinophil count NOS</td>
</tr>
<tr>
<td>42KZ</td>
<td>Eosinophil count NOS</td>
</tr>
<tr>
<td>Y7FAj</td>
<td>Eosinophil count NOS</td>
</tr>
<tr>
<td>42K3.00</td>
<td>Eosinophil count raised</td>
</tr>
<tr>
<td>42K3</td>
<td>Eosinophil count raised</td>
</tr>
<tr>
<td>42K3</td>
<td>Eosinophil count raised</td>
</tr>
<tr>
<td>Y7FAk</td>
<td>Eosinophil count raised</td>
</tr>
<tr>
<td>X001l1</td>
<td>Eosinophil non-allergic rhinit</td>
</tr>
<tr>
<td>Y02Rr</td>
<td>Eosinophil non-allergic rhinit</td>
</tr>
<tr>
<td>D403.00</td>
<td>Eosinophilia</td>
</tr>
<tr>
<td>D403</td>
<td>Eosinophilia</td>
</tr>
</tbody>
</table>
D403  Eosinophilia
Y20fr  Eosinophilia
D403z00  Eosinophilia NOS
D403z  Eosinophilia NOS
D403  Eosinophilia NOS
Y20fs  Eosinophilia NOS
Y20fq  Eosinophilic disorder
Y3017  Eosinophilicoesophagitis
X3009  Eosinophilicoesophagitis
Y108t  Eosinophilic pneumonia
4E32.11  Eosinophils: sputum
Y7FPs  Eosinophils: sputum
Y108u  EP - Eosinophilic pneumonia
Ya14p  EP-Acute eosinophil pneumonia
424.00  Full blood count - FBC
4243  Full blood count abnormal
4242  Full blood count borderline
4241  Full blood count normal
424Z.00  Full blood count NOS
Yaeib  Percentage eosinophil count
42b9.00  Percentage eosinophils
42b9.  Percentage eosinophils
42b9  Percentage eosinophils
Yaco9  Percentage eosinophils
XaCJj  Percentage eosinophils
Y108w  PIE - Pulinfil + eosinophilia
Y108v  Pulm infiltrate + eosinophilia
H583.00  Pulmonary eosinophilia
H583.  Pulmonary eosinophilia
H583  Pulmonary eosinophilia
Y108s  Pulmonary eosinophilia
H583z00  Pulmonary eosinophilia NOS
H583z  Pulmonary eosinophilia NOS
H583  Pulmonary eosinophilia NOS
Y108y  Pulmonary eosinophilia NOS
D4034  Secondary eosinophilia NOS
D403  Secondary eosinophilia NOS
D403400  Secondary eosinophilia NOS
Y20ft  Secondary eosinophilia NOS
Y1090  Simple pulmonary eosinophilia
4E32.00  Sputum: eosinophilia
4E32.  Sputum: eosinophilia
4E+32  Sputum: eosinophilia
Y7FPr  Sputum: eosinophilia
H583100  Tropical eosinophilia
H583  Tropical eosinophilia
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ya243</td>
<td>Tropical eosinophilia</td>
</tr>
<tr>
<td>H5831</td>
<td>Tropical eosinophilia</td>
</tr>
<tr>
<td>Y1099</td>
<td>Tropical pulm eosinophilia</td>
</tr>
<tr>
<td>Xa0kb</td>
<td>Tropical pulm eosinophilia</td>
</tr>
</tbody>
</table>
2b. Read code lists for childhood asthma

14B4.00 H/O: asthma
173A.00 Exercise induced asthma
173C.00 Occupational asthma
173D.00 Work aggravated asthma
178..00 Asthma trigger
1780 Aspirin induced asthma
1O2..00 Asthma confirmed
663..11 Asthma monitoring
663N.00 Asthma disturbing sleep
663N00
  o Asthma causing night waking
663N10
  o Asthma disturbs sleep weekly
663N20
  o Asthma disturbs sleep frequently
663O.00 Asthma not disturbing sleep
663O00
  o Asthma never disturbs sleep
663P.00 Asthma limiting activities
663Q.00 Asthma not limiting activities
663U.00 Asthma management plan given
663V.00 Asthma severity
663V00
  o Occasional asthma
663V10
  o Mild asthma
663V20
  o Moderate asthma
663V30
  o Severe asthma
663W.0
  o Asthma prophylactic medication used
  Emergency asthma admission since last
663d.00 appointment
663e.00 Asthma restricts exercise
6.63E+0
  2 Asthma sometimes restricts exercise
6.63E+1
  02 Asthma severely restricts exercise
663f.00 Asthma never restricts exercise
663j.00 Asthma - currently active
663m.0 Asthma accident and emergency attendance since
  last visit
663n.00 Asthma treatment compliance satisfactory
663p.00 Asthma treatment compliance unsatisfactory
663q.00 Asthma daytime symptoms
   Asthma causes night symptoms 1 to 2 times per
   month
663s.00 Asthma never causes daytime symptoms
   Asthma causes daytime symptoms 1 to 2 times per
   month
663t.00 Asthma causes daytime symptoms 1 to 2 times per
   week
663v.00 Asthma causes daytime symptoms most days
663w.00 Asthma limits walking up hills or stairs
663x.00 Asthma limits walking on the flat
663y.00 Number of asthma exacerbations in past year
66Y5.00 Change in asthma management plan
66Y9.00 Step up change in asthma management plan
66YA.00 Step down change in asthma management plan
66YC.00 Absent from work or school due to asthma
66YE.00 Asthma monitoring due
66YJ.00 Asthma annual review
66YK.00 Asthma follow-up
66YP.00 Asthma night-time symptoms
66YQ.00 Asthma monitoring by nurse
66YR.00 Asthma monitoring by doctor
679J.00 Health education - asthma
68C3.00 Asthma screening
8791 Further asthma - drug prevent.
8793 Asthma control step 0
8794 Asthma control step 1
8795 Asthma control step 2
8796 Asthma control step 3
8797 Asthma control step 4
8798 Asthma control step 5
8B3j.00 Asthma medication review
8CE2.00 Asthma leaflet given
8CR0.00 Asthma clinical management plan
8H2P.00 Emergency admission, asthma
9N1d.00 Seen in asthma clinic
9NI8.00 Asthma outreach clinic
9OJ.00 Asthma monitoring admin.
9OJ..1 Asthma clinic administration
9OJ1.00 Attends asthma monitoring
9OJ3.00 Asthma monitor offer default
9OJ4.00 Asthma monitor 1st letter
9OJ5.00 Asthma monitor 2nd letter
9OJ6.00 Asthma monitor 3rd letter
9OJ7.00  Asthma monitor verbal invite
9OJ8.00  Asthma monitor phone invite
9OJ9.00  Asthma monitoring deleted
9OJA.00  Asthma monitoring check done
9OJA.11  Asthma monitored
9OJZ.00  Asthma monitoring admin.NOS
9Q21.00  Patient in asthma study
9hA..00  Exception reporting: asthma quality indicators
         Excepted from asthma quality indicators: Patient
         unsuitable
         Excepted from asthma quality indicators: Informed
9hA2.00  dissent
H31200  Chronic asthmatic bronchitis
H33..00  Asthma
H33..11  Bronchial asthma
H330.00  Extrinsic (atopic) asthma
H330.11  Allergic asthma
H330.12  Childhood asthma
H330.13  Hay fever with asthma
H330.14  Pollen asthma
H33000  o  Extrinsic asthma - no status
H33000  o  Extrinsic asthma without status asthmaticus
H330011  Hay fever with asthma
H33010  o  Extrinsic asthma with status asthmaticus
H33010  o  Extrinsic asthma + status
H330111  Extrinsic asthma + attack
H330111  Extrinsic asthma with asthma attack
H330200  Extrinsic asthma NOS
H331.00  Intrinsic asthma
H331.11  Late onset asthma
H33100  o  Intrinsic asthma - no status
H33100  o  Intrinsic asthma without status asthmaticus
H331100  Intrinsic asthma + status
H331100  Intrinsic asthma with status asthmaticus
H331111  Intrinsic asthma + attack
H331111  Intrinsic asthma with asthma attack
H331200  Intrinsic asthma NOS
H332.00  Mixed asthma
H333.00  Acute exacerbation of asthma
H334.00  Brittle asthma
H33z.00  Asthma unspecified
H33z000  Status asthmaticus NOS
H33z011  Severe asthma attack
H33z100  Asthma attack
H33z111  Asthma attack NOS
H33z200  Late-onset asthma
H33z200  Asthma NOS
H33z211  Exercise induced asthma
H33z212  Allergic asthma NEC
H33z213  Allergic bronchitis NEC
H35y60  Sequoiosis (red-cedar asthma)
H35y700  Wood asthma
H47y00  Detergent asthma
SLF7200  Antiasthmatic poisoning NOS
TJF7.00  Adverse reaction to antiasthmatics
TJF7300  Adverse reaction to theophylline (asthma)
TJF7z00  Adverse reaction to antiasthmatic NOS
U60F60  [X] Antiasthmatics cause adverse effects in therapeutic use, NEC
U60F61  [X] Adverse reaction to theophylline - asthma
ZVu670  [X] Family history/asthma + other chronic lower resp diseases
2c. Read code lists for identifying atopy

### ALLERGIC RHINITIS CODES

<table>
<thead>
<tr>
<th>READ CODE</th>
<th>READ TERM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyu2100</td>
<td>[X]Other allergic rhinitis</td>
</tr>
<tr>
<td>H172.00</td>
<td>Allergic rhinitis NOS</td>
</tr>
<tr>
<td>H171.00</td>
<td>Allerg.rhinit.-other allergens</td>
</tr>
<tr>
<td>H17...00</td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>H172.00</td>
<td>Allergic rhinitis-unsp allerg</td>
</tr>
</tbody>
</table>

### ANIMAL ALLERGIES READ CODES

<table>
<thead>
<tr>
<th>READ CODE</th>
<th>READ TERM</th>
</tr>
</thead>
<tbody>
<tr>
<td>H171.11</td>
<td>Cat allergy</td>
</tr>
<tr>
<td>H171.12</td>
<td>Dander (animal) allergy</td>
</tr>
<tr>
<td>H171000</td>
<td>Allergy to animal</td>
</tr>
<tr>
<td>H171100</td>
<td>Dog allergy</td>
</tr>
<tr>
<td>14M4.00</td>
<td>H/O: cat allergy</td>
</tr>
</tbody>
</table>

### HAY FEVER READ CODES

<table>
<thead>
<tr>
<th>READ CODE</th>
<th>READ TERM</th>
</tr>
</thead>
<tbody>
<tr>
<td>H170.00</td>
<td>Allergic rhinitis - pollens</td>
</tr>
<tr>
<td>H170.11</td>
<td>Hay fever - pollens</td>
</tr>
<tr>
<td>H171.14</td>
<td>Hay fever - other allergen</td>
</tr>
<tr>
<td>H172.11</td>
<td>Hay fever - unspec allergen</td>
</tr>
<tr>
<td>Hyu2000</td>
<td>[X]Oth seasonal allergic rhinitis</td>
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</tbody>
</table>

### NASAL POLYP READ CODES

<table>
<thead>
<tr>
<th>READ CODE</th>
<th>READ TERM</th>
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</thead>
<tbody>
<tr>
<td>H11...00</td>
<td>Nasal polyps</td>
</tr>
<tr>
<td>H11y11</td>
<td>Nasal sinus polyps</td>
</tr>
<tr>
<td>2D33.00</td>
<td>O/E - nasal polyp present</td>
</tr>
<tr>
<td>H112.00</td>
<td>Nasal polyp NOS</td>
</tr>
<tr>
<td>7406000</td>
<td>Nasal polypectomy</td>
</tr>
<tr>
<td>H110200</td>
<td>Polyp of nasal cavity NOS</td>
</tr>
<tr>
<td>7416F00</td>
<td>FESS - polypectomy nasal sinus</td>
</tr>
<tr>
<td>H110200</td>
<td>Polyp of nasal cavity NOS</td>
</tr>
<tr>
<td>H11y100</td>
<td>Polyp of ethmoidal sinus</td>
</tr>
<tr>
<td>7402900</td>
<td>Excision polyp nasal septum</td>
</tr>
<tr>
<td>7402911</td>
<td>Nasal septum polypectomy</td>
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</tbody>
</table>
### CHRONIC RHINOSINUSITIS READ CODES

<table>
<thead>
<tr>
<th>READ CODE</th>
<th>READ TERM</th>
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<tbody>
<tr>
<td>H13..00</td>
<td>Chronic sinusitis</td>
</tr>
<tr>
<td>H13..11</td>
<td>Chronic rhinosinusitis</td>
</tr>
<tr>
<td>H130.00</td>
<td>Chronic maxillary sinusitis</td>
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<tr>
<td>H135.00</td>
<td>Recurrent sinusitis</td>
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<tr>
<td>H132.00</td>
<td>Chronic sinusitis NOS</td>
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</tbody>
</table>

### OTHER RHINITIS READ CODES

<table>
<thead>
<tr>
<th>READ CODE</th>
<th>READ TERM</th>
</tr>
</thead>
<tbody>
<tr>
<td>H120700</td>
<td>Chronic fibrinous rhinitis</td>
</tr>
<tr>
<td>H120200</td>
<td>Chronic rhinitis NOS</td>
</tr>
<tr>
<td>H120500</td>
<td>Chronic ulcerative rhinitis</td>
</tr>
<tr>
<td>H120600</td>
<td>Chronic membranous rhinitis</td>
</tr>
<tr>
<td>H17..11</td>
<td>Perennial rhinitis</td>
</tr>
<tr>
<td>H120400</td>
<td>Chronic infective rhinitis</td>
</tr>
<tr>
<td>H18..00</td>
<td>Vasomotor rhinitis</td>
</tr>
<tr>
<td>H00..16</td>
<td>Rhinitis - acute</td>
</tr>
<tr>
<td>H120000</td>
<td>Chronic rhinitis</td>
</tr>
<tr>
<td>H120000</td>
<td>Chronic simple rhinitis</td>
</tr>
<tr>
<td>H120300</td>
<td>Chronic atrophic rhinitis</td>
</tr>
<tr>
<td>H120200</td>
<td>Chronic hypertrophic rhinitis</td>
</tr>
<tr>
<td>H120100</td>
<td>Chronic catarrhal rhinitis</td>
</tr>
</tbody>
</table>

110 BM   ECZEMA MARGINATUM
6869MI  ECZEMA INFECTED
6869MP  ECZEMA IMPETIGINOUS
6869PL  ECZEMA PUSTULAR
691 EC  ECZEMA ATOTPIC
691 TM  ECZEMA WITH ASTHMA
6927EL  ECZEMA SOLARE
6929CE  ECZEMA
6929CF  ECZEMA RELAPSE
6929EE  ECZEMA ALLERGIC
6929EH  ECZEMA HAND(S)
6929ES  ECZEMA SCALP
6929H   ECZEMA DISCOID
6929LC  ECZEMA LICHENIFIED
6929NE  ECZEMA NUMMULAR
7059BE  ECZEMA POMPHOLYX
ECZEMA VACCINATION/VACCINATUM

FH: Eczema
H/O: eczema
Nipple eczema
Referral to eczema clinic

Ecema herpeticum - Kaposi’s
Ecema herpeticum - Kaposi’s varicelliform eruption
Thrombocytopenic eczema with immunodeficiency

No FH: Eczema

Eczematous eyelid dermatitis

Eczema of external ear
Asteatotic Eczema
Varicose veins of the leg with eczema
Varicose vein leg with eczema
Varicose eczema
Varicose veins of the leg with ulcer and eczema
Varicose vein leg+ulcer+eczema
Pustular eczema
Seborrhoeic eczema

Atopic dermatitis and related conditions
Infantile eczema
Flexural eczema
Allergic (intrinsic) eczema
Discoid eczema
Atopic dermatitis NOS

Eczema NOS
Discoid eczema
Infected eczema
Hand eczema
Erythrodermic eczema
[Dermatitis and eczema
Exacerbation of eczema
Atopic dermatitis/eczema