FP and Qvar Spacer vs Non-Spacer in Asthma

The use of a spacer in the delivery of large (Fluticasone Propionate) and small particle (Qvar®) inhaled corticosteroid (ICS) in asthma

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1 PRIMARY OBJECTIVE

The objective of this study is to investigate the real life effectiveness of ICS delivery of Fluticasone Propionate (FP) and Qvar® (beclomethasone dipropionate HFA) by pMDI with spacer compared to pMDI alone.

2 DATA SOURCE

This study will use the Optimum Patient Care Research Database (OPCRD) which comprises anonymous longitudinal data extracted from approximately 500 UK practices in order to perform reviews of their chronic respiratory services. OPCRD contains routine clinical data such as disease and prescribing information and patient reported outcomes collected via validated disease assessment questionnaires. The OPCRD has been approved by Trent Multi Centre Research Ethics Committee for clinical research use. Data will be supplemented with information from the Clinical Practice Research Database (CPRD), which is the computerized primary care
database funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA) containing anonymous longitudinal data extracted from approximately 600 practices throughout the UK.

The study will include patients aged 5-80 years, with evidence of current asthma\(^1\). Patients will be included if they have been prescribed either Qvar\(^\circledast\) (beclomethasone dipropionate HFA) or Fluticasone Propionate (FP) by pressurized metered dose inhaler (pMDI) with or without spacer at index prescription date with a minimum one year outcome period for effectiveness and adverse events. Patients must have a minimum of 12 months data prior to the index prescription date (as defined under ‘General Design and Methodology’) to allow patient characterization and confounder definition.

### 3 EXPOSURES

#### 3.1 INVESTIGATIONAL PRODUCT 1

Beclomethasone dipropionate HFA (Qvar\(^\circledast\)) is an extrafine particle corticosteroid used as asthma therapy. Two dose strengths are available in pMDI formulation: 50 and 100 µg per actuation.

#### 3.2 INVESTIGATIONAL PRODUCT 2

Fluticasone Propionate is a large particle topical corticosteroid used in the treatment of asthma or allergic rhinitis. The pMDI formulation includes three dose strengths: 50, 125 and 250µg per actuation.

#### 3.3 SPACER USE

Suboptimal pMDI use is a major issue in the treatment of asthma. A spacer is an add-on device designed to increase the ease of using pMDIs for patients. Using spacers in conjunction with pMDIs can increase the dose of ICS reaching the lungs and decrease the incidence of local side effects caused by ICS deposition at the back of the mouth and throat. However, spacers are not easily portable and are least preferred by patients\(^2\).

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\(^1\) Evidence of asthma diagnosis and receiving current asthma therapy, defined as ≥1 asthma prescriptions during the last 1 year.

Patients who were prescribed a spacer during baseline with their SABA inhaler will be assumed to use that spacer with their ICS in the outcome period and therefore will be included in the spacer arm (regardless of IPD / outcome spacer-prescribing).

4 GENERAL DESIGN AND METHODOLOGY

This study is a retrospective, effectiveness study consisting of a baseline and outcome period lasting a total of 24 months. The baseline period (for patient characterization and confounder definition) is the one-year prior to the index prescription date (IPD), at which point patients initiate treatment as:

1) a) FP delivered by pMDI with spacer, or  
   b) FP delivered by pMDI without spacer, or
2) a) Qvar® delivered by pMDI with spacer, or  
   b) Qvar® delivered by pMDI without spacer

Effectiveness outcomes over the one-year period following IPD will be compared between the treatments.

This study population will be divided into an adult cohort and a pediatric cohort.

Figure 1. Study design
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5 PATIENT CRITERIA

5.1 CRITERIA FOR INCLUSION

- Age at index prescription date:
  - 5-11 years (pediatric cohort)
  - 12-80 years (adult cohort)
- Evidence of current asthma, as defined by an asthma diagnosis AND/OR current asthma therapy (≥1 asthma prescriptions during the last 1 year)
- only 1 prescription for Qvar® or FP at IPD
- At least two years of continuous data (consisting a minimum of 1 year of data prior and minimum 1 year post IPD)
- Continuation of Qvar or FP therapy (≥ 2 prescriptions during the outcome year including IPD prescription)

5.2 CRITERIA FOR EXCLUSION

- Any chronic respiratory disease, except asthma
- Maintenance oral steroids during baseline year
- For patients aged 60-80 years old: any smoking history (as they might be misdiagnosed COPD patients)
- Start other asthma therapies than ICS on IPD

6 STUDY ENDPOINTS

6.1 PRIMARY ENDPOINT

6.1.1 EXACERBATION DEFINITION BASED ON THE AMERICAN THORACIC SOCIETY (ATS)/ EUROPEAN RESPIRATORY SOCIETY (ERS) TASK FORCE DEFINITION

An exacerbation is defined as an occurrence of the following:

1. Asthma-related:
   a. Hospital admissions OR

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3 Where ≥1 oral steroid course / hospitalisation occurs within 2 weeks of each other, these events will be considered to be the result of the same exacerbation (and will only be counted once).

4 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).
6.2 SECONDARY ENDPOINTS

6.2.1 EXACERBATION DEFINITION BASED ON CLINICAL EXPERIENCE
An exacerbation is defined as an occurrence of the following:

1. Asthma-related:
   a. Hospital admissions OR
   b. A&E attendance; OR
2. An acute course of oral steroids with evidence of respiratory review; OR
3. Antibiotics prescribed with evidence of a respiratory review.

6.2.2 RISK DOMAIN ASTHMA CONTROL (RDAC)
RDAC status can either be:

Controlled: absence of the following:

1. Asthma-related:
   a. Hospital admission AND
   b. A&E attendance, AND
   c. Out-patient department attendance; AND
2. Acute use of oral steroids with evidence of respiratory review; OR
3. Antibiotics prescribed with evidence of a respiratory review.

Uncontrolled: all others.

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5 Acute oral steroid use associated with asthma exacerbation treatment will be defined as:
   - all courses that are definitely not maintenance therapy, and/or
   - all courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed), and/or
   - all courses with no dosing instructions, but unlikely to be maintenance therapy with a code for asthma or a lower respiratory event

where "maintenance therapy" is defined as: daily dosing instructions of <10mg Prednisolone or prescriptions for 1mg Prednisolone tablets.

6 Where ≥1 oral steroid course / hospitalisation / antibiotics prescription occur within 2 weeks of each other, these events will be considered to be the result of the same exacerbation (and will only be counted once).

7 Evidence of a Respiratory Review - 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, COPD and LRTI read codes);
   b) Asthma/COPD review codes excl. any monitoring letter codes;
   c) Lung function and/or asthma monitoring.

8 May be called exacerbation control in the future to differentiate from Asthma Control Test (ACT) / Asthma Control Questionnaire (ACQ) measures of asthma control.
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6.2.3 OVERALL ASTHMA CONTROL (OAC) – RISK AND IMPAIRMENT
OAC status can either be:

**Controlled:**
1. Achieved Risk Domain Asthma Control (as defined above) AND
2. Average daily dose of:
   a. UK: ≤200mcg salbutamol / ≤500mcg terbutaline
   b. USA: ≤180mcg salbutamol / albuterol or ≤500mcg terbutaline.

**Uncontrolled:** all others.

6.2.4 TREATMENT STABILITY
Treatment is considered as either:

**Stable:**
1. Achieved Risk Domain Asthma Control (as defined above); AND
2. No additional therapy
   a. Increased dose of ICS (≥50% increase of that prescribed at index date) AND/OR
   b. Use of additional therapy as defined by: long-acting bronchodilator (LABA), theophylline, leukotriene receptor antagonists (LTRAs).

**Unstable:** all others.

**Note.** This excludes changes in therapeutic regimen that are likely to be motivated by cost-savings.

6.2.5 SHORT ACTING BRONCHODILATOR (SABA) USAGE
Average daily SABA dosage during outcome year, calculated as average number of puffs per day over the year multiplied by strength (in mcg);

\[
\text{i.e. } \frac{\text{Number of inhalers} \times \text{doses per inhaler}}{365} \times \text{strength}
\]

and categorised as appropriate to the data.
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6.2.6 Lower respiratory-related hospitalisations

A lower-respiratory hospitalisation can be considered as:

- **Definite**: Hospitalisations coded with a lower respiratory code, including asthma and LRTI codes; OR a generic hospitalisation read code which has been recorded on the same day as a Lower Respiratory Consultation⁹;
- **Definite + Probable**: Hospitalisations occurring within a 7-day window (either side of the hospitalisation date) of a lower respiratory read code.

6.2.7 Adherence to therapy

Adherence can be calculated as follows:

**Number days per pack** = Number of actuations per pack / Number of actuations per day

**Total Pack Days** = \(\Sigma\) (Number days per pack)

**Refill Rate %** = (Total pack days/365) * 100

6.2.8 Incidence of oral thrush

**First definition:**
1. Topical anti-fungal prescriptions **definitely** for oral thrush; AND/OR
2. Coded for oral candidiasis.

**Second definition:**
1. Topical anti-fungal prescriptions **definitely or possibly** for oral thrush; AND/OR
2. Coded for oral candidiasis.

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⁹Lower Respiratory Consultations - consist of the following:

a) Lower Respiratory read codes (including Asthma, COPD and LRTI read codes);
b) Asthma/COPD review codes excl. any monitoring letter codes;
c) Asthma monitoring.
7 STATISTICAL ANALYSIS PLAN

7.1 GENERAL
All analyses will be carried out using IBM SPSS Statistics version 21\(^1\), SAS version 9.3\(^2\) and Microsoft Office EXCEL 2007.

7.2 EXPLORATORY ANALYSIS

SUMMARY STATISTICS: Summary statistics will be produced for all baseline and outcome variables, as a complete dataset and by treatment. For variables measured on the interval or ratio scale, these will include:

- Sample size (n) & percentage non-missing
- Mean & Variance / Standard Deviation
- Range (Minimum / Maximum)
- Median & Inter-quartile Range (25th and 75th percentiles)
- Frequency distribution plots

For categorical variables, the summary statistics will include:

- Sample size (n)
- Range (if applicable)
- Count and Percentage by category (distribution)
- Bar charts

COVARIATES: Prior research in respiratory disease has identified a range of potential confounders that may impact on study outcomes. These include a range of demographic, disease severity, treatment and co-morbid factors. These variables will be extracted, where available, for all patients.

1) Potential confounders examined at (or closest to) the relevant index date:

- Age of patient
- A marker of socio-economic status where possible, i.e. post codes
- Gender of patient
- Height of patient
- Weight of patient
- Body Mass Index (BMI) (in sub-group where BMI can be evaluated)
- Lung function, in terms of percent predicted peak flow readings (PEF) prior to index date
- Smoking status
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2) Potential confounders examined regardless of when they occurred relative to the index date:
   - Date of first asthma diagnosis

3) Potential confounders examined in the year before the index prescription date:
   - Presence / absence of comorbid rhinitis (diagnosis ever and / or prescriptions for rhinitis therapy in the prior/outcome year
   - Where rhinitis is present, use of nasal steroids for its treatment.
   - Presence / absence of comorbid eczema (diagnosis ever and / or prescriptions for eczema therapy in the prior/outcome year
   - Preschool wheeze diagnosis¹⁰ (Paediatric only)
   - Preschool asthma diagnosis (asthma read code and/or prescriptions between the age of 1 up to 3) (Paediatric only)
   - Other important unrelated co-morbidities will be expressed using the Charlson Comorbidity Index (CCI)
   - Presence of GERD (diagnosis ever and / or prescriptions for GERD therapy in the prior/outcome year
   - Presence of cardiac disease (diagnosis ever and / or prescriptions for cardiac drugs in the prior /outcome year
   - Possible atopy¹¹
   - Number of hospital outpatient attendances where asthma is recorded as the reason for referral
   - Number of hospitalisations for asthma or possibly respiratory related (a non-specific hospitalisation code and an asthma / respiratory code within a one week window).
   - Number of prescriptions for any antibiotic with evidence for respiratory review
   - Other medications, number of prescriptions for the following in the year prior to IPD:
     - Paracetamol
     - Non-steroidal anti-inflammatory drugs (NSAIDs)
     - Beta-blocker prescriptions
     - Theophylline
     - Statins
     - Tricyclics
   - Number of prescriptions for any respiratory therapy (split by number of prescriptions for each) in the prior year.
   - Number of exacerbations for asthma in year preceding assessment.
   - Number of general practice consultations for asthma that did not result in asthma exacerbations treatment.

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¹⁰ When a patient had a wheeze code recorded between the age of 1 up to 3
¹¹ Defined as: Presence of rhinitis diagnosis &/or therapy; AND/OR Presence of eczema diagnosis &/or therapy.
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- Number of short-acting beta-agonist (SABA) prescriptions received in the prior year (calculated based on total combined dose of refilled prescriptions and averaged over 365 days).
- Asthma consultations
- Primary care consultations
- Non asthma consultations
- Singulair scripts
- Oral Steroids (OS) courses
- ICS dose prescribed at index date.
- Controller-to-reliever therapy ratio.
- Oral thrush.

DATA PREPARATION: The data will be prepared for analysis by:

- Investigating potential outliers;
- Identifying and creating new variables as necessary:
  - Transformations of skewed data (for example, log transformations);
  - Categorisation of heavily skewed data;
- Investigating missing data (type of and reason for missingness).

7.3 BASELINE ANALYSIS

Summary statistics will highlight differences in baseline variable distributions between treatment groups. These differences will be quantified using conditional logistic regression models. Treatment arms will be compared using t-test / Mann Whitney U-test (depending on distribution) for variables measured on the interval/ratio scale and using a chi square test for categorical variables.

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

PREDICTORS OF OUTCOMES: Multivariate analyses will be carried out using the full dataset and each data split to identify baseline variables that are predictive (\( p < 0.05 \)) of each outcome variable during the outcome period. These will be considered as potential confounders when modelling the outcome variables.

CORRELATIONS: Spearman correlation coefficients will be calculated between all potential confounders to determine strengths of linear relationships between variables. The correlation coefficients will be considered - in conjunction with clinical interpretation - to identify pairings of variables that may present collinearity issues at
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the modelling stage. Scatter plots and error bars may be used to further investigate relationships.

PATIENT MATCHING: CASE-CONTROLLED DESIGN: If the exploratory analysis shows significant differences between the cohorts prior to IPD, patients will be matched at IPD for key baseline characteristics; the matching criteria and matching ratio will be determined once the baseline data have been examined. Baseline characterisation will be via demographic and clinical variables (e.g. age, gender, baseline exacerbations / acute oral steroid use.) Any residual differences between the treatment arms after matching that are considered to be potentially significant (p<0.10) and any variables predictive of the outcome will be adjusted for through further statistical modelling. When items are co-linear in nature clinical input will be sought to decide which variable of those that are co-linear are put into the model.

7.4 OUTCOME ANALYSES

7.4.1 UNADJUSTED COMPARISONS

7.4.1.1 PRIMARY OUTCOME:
The numbers and percentages of patients within each treatment group with 0, 1 and ≥2 recorded exacerbations (ATS definition) during the outcome period will be calculated and tabulated. Chi square tests, or conditional logistic regression in case treatment groups require matching, may be used to compare the distribution of exacerbations between treatment groups and a p-value reported.

7.4.1.2 SECONDARY OUTCOMES
The numbers and percentages of patients within each treatment group with 0, 1 and ≥2 recorded exacerbations (definition based on clinical experience) during the outcome period will be calculated and tabulated. Chi square tests, or conditional logistic regression in case treatment groups require matching, may be used to compare the distribution of exacerbations between treatment groups and a p-value reported.

The numbers and percentages of patients within each treatment group achieving asthma control (both definitions) will be calculated and tabulated. Chi square tests, or conditional logistic regression in case treatment groups require matching, may be used to compare the unadjusted proportions achieving control.

The numbers and percentages of patients within each treatment group achieving treatment stability will be calculated and tabulated. Chi square tests, or conditional
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logistic regression in case treatment groups require matching, may be used to compare the unadjusted proportions achieving stability.

The numbers and percentages of patients within each treatment group with 0 and ≥1 recorded hospitalisation during the outcome period will be calculated and tabulated. Chi square tests, or conditional logistic regression in case treatment groups require matching, may be used to compare the distribution of hospitalisations between treatment groups and p-values reported.

The numbers and percentages of patients within each treatment group recording adherence to ICS therapy of <50%, 50-<70%, 70-<100%, ≥100% will be calculated and tabulated. Chi square tests, or conditional logistic regression in case treatment groups require matching, may be used to compare the distribution of adherence between treatment groups and a p-value reported.

The numbers and percentages of patients within each treatment group recording SABA dosages of 0mcg, >0-100mcg, >100-200mcg, >200-400mcg and >400mcg will be calculated and tabulated. Categorisations may be revised subject to exploratory analysis of the data. Chi square tests, or conditional logistic regression in case treatment groups require matching, may be used to compare the distribution of SABA usage between treatment groups and a p-value reported.

7.4.1.3 DISAGGREGATED RESULTS

The disaggregated components of the composite primary and secondary outcomes will be presented as unadjusted results. These include: hospitalisations for asthma-related events (YES/NO); Prescription of antibiotics with evidence of respiratory review (YES/NO); Prescription of oral steroids with evidence of respiratory review (YES/NO); SABA Dosage (≤200mcg / >200mcg); Increase in ICS Dose (YES/NO); and Additional Therapy (YES/NO). P-values (calculated using Chi square tests or conditional logistic regression in case treatment groups require matching) will be presented to quantify any differences between treatment groups.

7.4.2 ADJUSTED COMPARISONS

7.4.2.1 PRIMARY ENDPOINT: EXACERBATIONS (ATS DEFINITION)

The total number of exacerbations (ATS definition) in the outcome period will be compared between treatment groups. A Poisson regression model will be used to obtain an estimate of relative exacerbation rates. The model will use a robust estimator of the covariance matrix for more conservative confidence interval estimates. If treatment groups require matching, a conditional Poisson regression model will be used instead, using empirical standard errors (for more conservative
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confidence interval estimations) and adjustments will be made for potential baseline confounders.

Those variables that were significantly different or showed a trend towards a difference (p < 0.10) between the treatment groups at baseline will be included as potential confounding factors. In addition, variables that are found to be predictive (p < 0.05) of the outcome through multivariate analysis will also be considered as potential confounders. Results will be reported as adjusted odds ratios (95% CI) for QVAR/FP with spacer relative to QVAR/FP without spacer (reference arm).

### 7.4.2.2 SECONDARY ENDPOINTS:

**CLINICAL EXACERBATIONS:** The total number of exacerbations (clinical definition) in the outcome period will be compared between treatment groups. A Poisson regression model will be used to obtain an estimate of relative exacerbation rates. The model will use a robust estimator of the covariance matrix for more conservative confidence interval estimates. If treatment groups require matching, a conditional Poisson regression model will be used instead, using empirical standard errors (for more conservative confidence interval estimations) and adjustments will be made for potential baseline confounders.

**RISK DOMAIN ASTHMA CONTROL (RDAC), AND OVERALL ASTHMA CONTROL (OAC):** The adjusted odds of achieving asthma control (both definitions) will be compared between treatment groups using logistic regression models, or conditional binary logistic regression models if treatment groups require matching. Asthma control status will be used as the dependent variable with treatment and potential confounding factors as explanatory variables.

**TREATMENT STABILITY:** The adjusted odds of achieving treatment stability will be compared between treatment groups using logistic regression models, or conditional binary logistic regression models if treatment groups require matching. Treatment stability status will be used as the dependent variable with treatment and potential confounding factors as explanatory variables.

**SHORT ACTING BRONchodilATOR (SABA) USAGE:** The adjusted odds of being in a higher SABA usage category will be compared between treatment groups using ordinal regression models, or conditional ordinal logistic regression models if treatment groups require matching. The SABA category will be used as the dependent variable with treatment and potential confounding factors as explanatory variables.

**LOWER RESPIRATORY-RELATED HOSPITALISATIONS:** Where event numbers are sufficient, the total number of hospitalisations in the outcome period will be compared between treatment groups using a Poisson regression model, or a conditional Poisson regression model if treatment groups require matching to obtain
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an estimate of relative hospitalisation rates. The model will use empirical standard errors (for more conservative confidence interval estimations) and adjustments will be made for potential baseline confounders.

**ADHERENCE:** The adjusted odds of being in a higher **adherence** category will be compared between treatment groups using ordinal regression models, or conditional ordinal logistic regression models if treatment groups require matching. The adherence category will be used as the dependent variable with treatment and potential confounding factors as explanatory variables.

**ORAL THRUSH:** The total number of **incidents of oral thrush** in the outcome period will be compared between treatment groups using a Poisson regression model, or a conditional Poisson regression model if treatment groups require matching to obtain an estimate of relative incident rates of oral thrush. The model will use empirical standard errors (for more conservative confidence interval estimations) and adjustments will be made for potential baseline confounders.

Those variables that were significantly different or showed a trend towards a difference (p < 0.10) between the treatment groups at baseline will be included as potential confounding factors. In addition, variables that are found to be predictive (p < 0.05) of the outcome through multivariate analysis will also be considered as potential confounders. Results will be reported as adjusted odds ratios (95% CI) for QVAR/FP with spacer relative to QVAR/FP without spacer (reference arm).

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**8 STEERING COMMITTEE**

An independent steering committee would review baseline data and advise on the appropriate analysis plan (e.g. appropriate matching criteria). Recommendations for the study’s steering committee are welcomed from the study sponsor. Steering committees can include one medical representative from the sponsoring company who will be listed on any study-related publications (e.g. abstracts, posters, manuscripts).

The expert steering committee will review the baseline data and advise (a priori) on the statistical analysis plan. Interim study meetings will be held with the steering committee and Teva representatives at key milestones (e.g. baseline data review, outcome data review, publication planning) via teleconferencing and webex facilities and / or face-to-face as appropriate.

The information study findings will be disseminated for the benefit of the research fraternity through abstract presentation at appropriate respiratory conferences and peer reviewed respiratory journals (preferred congresses and titles will be agreed with study sponsor).
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9 TIMELINES

We aim to have some results to discuss at the small airway study group on 30th June.

<table>
<thead>
<tr>
<th>Action</th>
<th>Timeline</th>
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<tbody>
<tr>
<td>Data Extraction &amp; Exploratory analysis</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Outcome analysis</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Report writing</td>
<td>2 weeks</td>
</tr>
<tr>
<td>First draft of paper</td>
<td>4-6 weeks from final report</td>
</tr>
</tbody>
</table>

10 RESEARCH TEAM

Chief Investigator: Professor David Price, Professor of Primary Care Respiratory Medicine and Director of Research in Real Life

Research Team

- Project Director: Catherine Hutton
- Project Coordinator: Victoria Carter
- Senior Statistician: Annie Burden
- Statistics Team: Vicky Thomas, Kathryn Richardson and Muzammil Ali
- Senior Data Analyst: Julie von Ziegenweidt
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• Researcher: Alice Durieux

REFERENCES
