Study protocol

Stage 3: Real-life effectiveness and cost impact evaluation of fixed dose combination fluticasone propionate/formoterol (Flutiform®) compared with fluticasone propionate/salmeterol

Historical observational cohort, UK database study comparing clinical effectiveness, cost effectiveness and safety of combination fluticasone propionate/formoterol (Flutiform®) with combination fluticasone propionate/salmeterol in adult patients with active asthma: Stage 3

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Medicinal product	Fluticasone propionate/formoterol (Flutiform®) 50/5 µg pMDI, 125/5µg pMDI, 250/10 µg pMDI Fluticasone propionate/salmeterol (Seretide®) 50/25 µg pMDI, 100/50 µg DPI, 125/25 µg pMDI, 250/25 µg pMDI, 250/50 µg DPI, 500/50 µg DPI
Marketing authorisation holder	Napp Pharmaceuticals
Study aims and objectives	To investigate the non-inferiority and cost effectiveness of equivalent doses of combination fluticasone propionate/formoterol (Flutiform®) versus combination fluticasone propionate/salmeterol (Seretide®) in adult patients with active asthma
Country of study	United Kingdom
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1 Background

Asthma is a major cause of disability and mortality with an estimated global prevalence of 4.3% based on data from the World Health Organisation [1]. In addition to the health burden on patients, it also represents a considerable financial burden through direct costs (including prescription costs, primary care consultations, inpatient admissions, outpatient consultations and accident and emergency visits) and indirect costs (including travel costs, lost workdays and lost productivity)[2].

In patients with asthma not currently controlled by inhaled corticosteroids (ICS) and short acting $beta_2$ agonists (SABA) alone, current Global Initiative for Asthma (GINA) guidelines recommend the addition of a long-acting beta agonist (LABA) as a step-up option[3]. The combination of ICS and LABA provides both bronchodilatory and complimentary anti-inflammatory effects[4]. ICS/LABA treatments have been demonstrated to be more effective over the first 12 weeks of treatment when delivered as a fixed dose combination (FDC) over their equivalent mono-components[5,6].

The Salmeterol Multicenter Asthma Research Trial (SMART) concluded that LABA therapy alone increases severe asthma exacerbations[7]. The combination of LABA plus ICS in a single inhaler has been shown to improve adherence to therapy[8,9] while being as safe and more clinically effective than ICS treatment alone[10,11].

Despite the use of combination LABA/ICS treatment, the prevalence of uncontrolled asthma has remained stubbornly high. The factors behind sub-optimal asthma control include both poor patient adherence and incorrect inhaler technique. The adherence rate to asthma inhalers has been estimated at 22-63%[10,11,12] while the number of asthma patients that demonstrate correct inhaler technique has been estimated to be as low as 17-42%[13,14]. The number of patients that are motivated to collect their inhalers is also low in some regions, with the prescription coverage of ICS/LABA inhalers being estimated at 25% in a recent US study[10]. With these alarmingly poor figures, it is not surprising that a recent series of studies have showed that 50% of patients in the United Kingdom have sub-optimal disease control[15] despite increasing numbers of asthma prescriptions[16]. There is significant potential for improvement of asthma control if adherence and inhaler technique is improved[17]. In addition to prescribing the correct medication according to the GINA guidelines, practitioners should also consider prescribing the device that is most likely to deliver the drug to the desired site of action, and encourages better adherence to proper inhaler technique.

Early randomised controlled trial data suggest that fluticasone propionate/formoterol (FP/FOR) is as effective in terms of improvement in forced expiratory volume (FEV_1) compared with fluticasone propionate/salmeterol (FP/SAL)[18,19]. In addition, the design of the FP/FOR inhaler and characteristics of the aerosol has the potential to offer benefits in adherence and drug delivery. This is supported by prior real-life observational studies which have demonstrated the numerical superiority of FP/FOR compared to FP/SAL in terms of reducing severe asthma exacerbations[20].

Initial perception of medication efficacy has been shown to be important in inhaler adherence[21]. FP/FOR has a more rapid onset of action while retaining a similar adverse event profile[19] providing a greater perception of medication benefit which may in turn improve inhaler adherence.

Consistent use of inhaled corticosteroids in asthma is important to protect against death, hospitalisation and exacerbations[22,23,24]. The FP/FOR pressurised metered dose inhaler (pMDI) has a dose counter which has the potential of reducing missed doses when patients activate an empty inhaler. The presence of a dose counter on inhaler devices has been shown to reduce incidence of respiratory related emergency room visits[25], as well as improving satisfaction with their inhaled delivery device[26].

There has been considerable interest in the effect of particle size on lung deposition and the potential beneficial effects on clinical outcomes by targeting areas of inflammation. Pharmacokinetic studies have demonstrated that inhaled corticosteroids with high fine particle fractions (FPF) are associated with greater levels of lung deposition than those with larger particle fractions[27] especially in the small airways. Finer ICS particle sizes have also been identified in real life studies as resulting in better asthma control[28]. Smaller $beta_2$-agonist particle sizes have been demonstrated to achieve a more uniform lung distribution[29] which suggests that ICS/LABA combinations with a higher FPF fraction would be able to achieve greater deposition than large particle ICS/LABA inhalers.

The most beneficial effect of finer particles may occur in particular asthma subpopulations such as current smokers (who are generally excluded from randomised clinical trials) and those with more severe disease. Smaller ICS particles have been shown to contribute to improved asthma and higher FEVs in smoking populations[30]. The increased efficacy of fine particle formulations in smokers may be due to better distribution in the presence of inflamed small airways. The small airways contain both $beta_2$ and corticosteroid receptors, allowing

more widely distributed inhaled therapies to have a potentially more widespread pharmacological effect[31].

Although the small airways were once considered to be less relevant in all but the most severe disease because of the large airway reserve, there is now a considerable body of evidence that indicates that asthma control is significantly influenced by small airways disease[32].

Fluticasone/formoterol metered dose inhalers (FP/FOR pMDI) have been shown to provide a higher fine particle fraction of fluticasone and formoterol (41.2% and 39.2% respectively) compared to other delivery devices used for asthma patients including fluticasone/salmeterol dry powder inhalers (FP/SAL DPI has been shown to have a lower fine particle fraction of 12.5% fluticasone propionate and 11.3% salmeterol). In addition, the FPF of Flutiform® is consistent at different flow rates (as experienced when patients incorrectly inhale too forcefully or gently) promoting the consistency of drug deposition despite differences in patient inhalation techniques[33].

An additional consideration to inhaler design are the characteristics of the propellant and the design of the mouthpiece, both of which affect plume velocity. Plume velocity affects lung deposition and has also been demonstrated to influence inertial impaction in the oropharynx with higher velocities and larger particle size associated with increased impaction and throat discomfort[34]. Inhaled corticosteroids that are deposited in the oropharynx do not reach the site of action, can cause side effects such as oral candidiasis and be systemically absorbed when swallowed. Some propellants used in pMDIs produce forceful and cold plumes that can cause discomfort and have the potential to reduce adherence[35]. The FP/FOR pMDI provides a lower plume velocity and longer warm plume duration than FP/SAL pMDI[36] delivering more of the drug to the lungs with less potential for discomfort and side effects.

Equivalency or superiority of FP/FOR over FP/SAL in clinical practice would make adoption of FP/FOR an attractive proposition because of the current cost advantages of prescribing the FP/FOR fixed dose inhaler as shown in Table 1.

Table 1: Comparative costs of FP/FOR and FP/SAL[37]

Fluticasone propionate dosage (µg)	Cost per 120 FP/FOR dose inhaler (£)	Cost per 120 FP/SAL dose inhaler (£)
50	18.00	18.00
125	29.26	35.00
250	45.56	59.48

Thus, further study is required regarding the clinical implications of the prescription of FP/FOR in place of FP/SAL on clinical effectiveness and cost impact in patients with asthma.

2 Study aims and objectives

2.1 Study aims

The aim of this stage 3 study is to examine the real life effectiveness and cost impact outcomes between FP/FOR and FP/SAL.

2.2 Study objectives

2.2.1 Primary objective

To examine non-inferiority of effectiveness (in terms of the proportion with 'no exacerbations' [ATS/ERS Task Force definition]) of fluticasone propionate / formoterol (Flutiform®; FP/FOR) relative to fluticasone propionate / salmeterol (Seretide®; FP/SAL) in matched patients from two cohorts of patients with asthma.

If the non-inferiority criteria is met, this objective will expand to an assessment of the number of exacerbations observed in patients on fluticasone propionate / formoterol (Flutiform®; FP/FOR) compared with fluticasone propionate / salmeterol (Seretide®; FP/SAL).

2.2.2 Secondary objectives

To evaluate comparative effectiveness and cost impact outcomes of fluticasone propionate / formoterol (Flutiform®; FP/FOR) relative to fluticasone propionate / salmeterol (Seretide®; FP/SAL) in matched patients from two cohorts of patients with asthma.

3 Study design

3.1 Products studied

Flutiform® is a combination therapy that is licensed for use in the United Kingdom for patients 12 years and over when the combination of ICS and LABA is appropriate[38]. The inhaler combines fluticasone propionate with formoterol in a pressurised metered dose aerosol inhaler (pMDI) with a patient facing dose counter. Flutiform® is licensed in the UK for the regular treatment of asthma in patients aged 12 years and over (50/5 µg and 125/5 µg strengths) and in 250/10 µg strength for 18 years and over[39].

Seretide® is a combination therapy consisting of fluticasone propionate and salmeterol[40]. It is delivered in an Evohaler® (pMDI) device. The Evohaler® is available in 50/25 µg, 125/25 µg or 250/25 µg strengths. The Accuhaler® is available in 100/50 µg, 250/50 µg and 500/50 µg. Seretide is indicated in the regular treatment of patients aged in the regular treatment of patients aged 4 years and over with asthma where use of a combination product (LABA plus ICS) is indicated[41].

3.2 Study design

This is a matched historical cohort study of real life effectiveness and cost impact evaluation of Flutiform® (FP/FOR) and Seretide® (FP/SAL) over a 12 month period after the index date (i.e. the date of first FDC prescription as either FP/FOR or FP/SAL).

Two cohorts will be evaluated: the initiation cohort and change cohort:

(i) Initiation cohort:

ICS patients who, at index date, receive their first FDC ICS/LABA prescription as:

- FP/FOR pMDI, or
- FP/SAL pMDI
- After the index date receive ≥2 prescriptions for FDC ICS/LABA (ie: at least 3 prescriptions in total for FDC ICS/LABA)

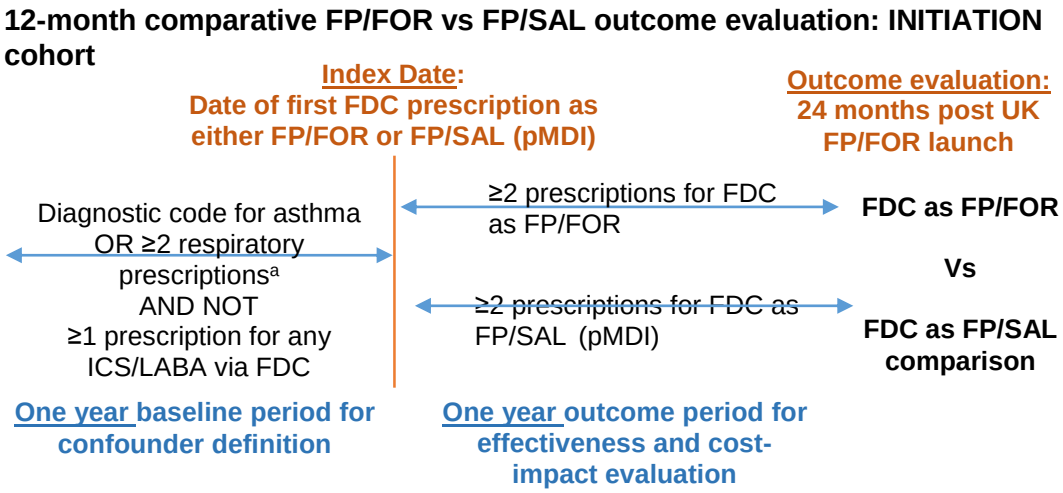

Figure 1: Initiation cohort

Initiation cohort patients will have received ≥2 respiratory prescriptions[a] during the baseline year. They will have received no prescriptions for combined ICS/LABA during the baseline year.

[a] See section 14.1 for definitions

(ii) Change cohort:

FP/SAL (pMDI) patients who, at the index date, receive either:

- A repeat prescription for FP/SAL pMDI therapy without a change in ICS daily dose
- AND after index date receive ≥2 prescriptions for FDC ICS/LABA (ie: at least 3 prescriptions in total for FDC ICS/LABA)
- OR first prescription for FP/FOR at index date at the same ICS dose as last FP/SAL prescription followed by ≥2 prescriptions for FP/FOR

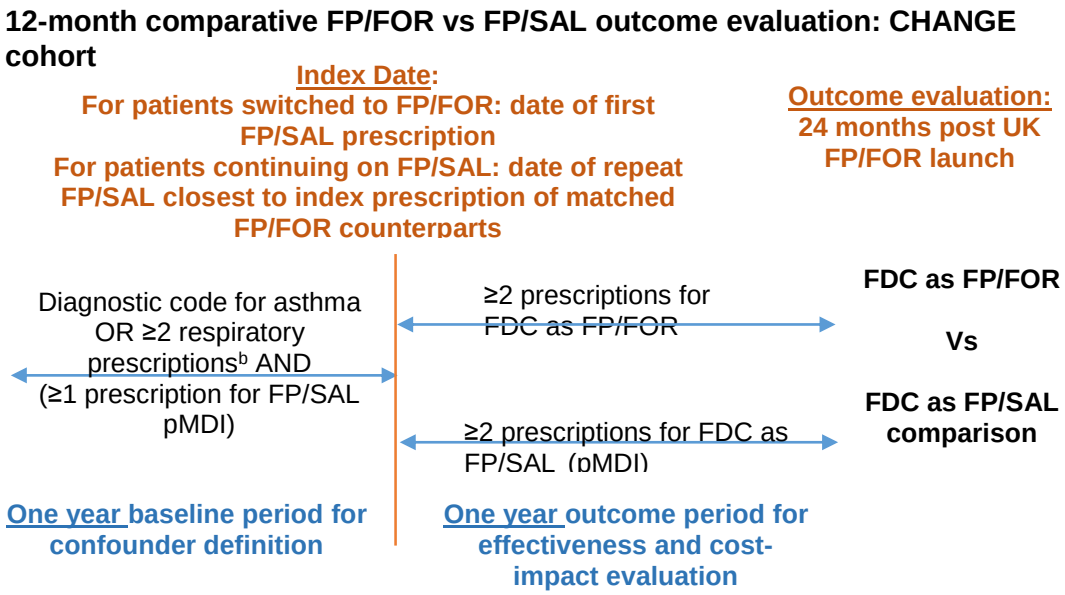

Figure 2: Change cohort

Change cohort patients will have at least one year of complete history with ≥ 1 prescription for ICS/LABA combination therapy for FP/SAL with a diagnostic code for asthma OR ≥ 2 respiratory prescriptions[b] AND one year of complete history post index date with ≥ 2 prescription for FP/FOR or FP/SAL.

[b] as defined in Section 14.1

Each patient treated with FP/FOR in the initiation and change cohorts will be matched against 4 patients treated with FP/SAL to increase the power of the study to demonstrate the effectiveness of FP/FOR vs FP/SAL. Initiation and change will be used as a matching variable. Analysis will be performed on all patients for primary and secondary outcomes, with a repeat analysis for subgroups. The primary outcome will be for the combined treatment groups (FP/SAL, FP/FOR) across initiation and change cohorts.

4 Study population

4.1 Inclusion and exclusion criteria

Inclusion criteria

To be included in the study dataset, patients must meet the following criteria:

(i) Age: 12–80 years

(ii) Evidence of active asthma, defined as a diagnostic code and/or ≥2 prescriptions for asthma therapy during the baseline

- **Initiation cohort**: patients must NOT have received ≥1 ICS/LABA prescription via fixed dose combination inhaler during baseline
- **Change cohort**: patients must have received ≥1 FDC FP/SAL (pMDI) prescription during baseline.

(iii) **Evidence of continued asthma treatment**: ≥2 FP/FOR prescriptions during the outcome period for treatment groups exclusive of prescription at index date, or : ≥2 FP/SAL prescriptions for control groups exclusive of prescription at index date

(iv) **Continuous records:** at least one year of baseline data before index date and at least one year of outcome data after index date.

(v) All FP/FOR patients must be registered at practices considered to have a policy of FP/FOR adoption or wholesale change. Such practices will be identified as those at which ≥5 patients initiate on FP/FOR or change from existing FDC ICS/LABA (any) therapy to FP/FOR within a three-month period.

Exclusion criteria

Patients were excluded from the study if they met the following criteria:

(i) Had any chronic respiratory disease (e.g. chronic obstructive pulmonary disease [COPD]) other than asthma at any time
(ii) Received maintenance oral corticosteroid therapy during the baseline period
(iii) Received multiple FDC ICS/LABA or separate ICS or LABA prescriptions at the initiation of FP/FOR

5 Data source

Optimum Patient Care (OPC) extracts anonymous data from practices to perform reviews of their chronic respiratory services. OPC software interfaces with primary care practice management systems and extracts detailed clinical, therapy and referral information. The service provides dates and measurements for demographics, chronic disease status, acute diagnosis, consultations, hospitalisations, drug costs, prescriptions and clinical measurements that is regularly updated and stored as the Optimum Patient Care Research Database (OPCRD).

The OPCRD has been approved by Trent Multi Centre Research Ethics Committee for clinical research use. The database includes data from over a million patients captured across more than 520 practices as of April 2015.

The anonymised, longitudinal patient data offers a high-quality data source for use in clinical, epidemiological and pharmaceutical research. It enables research to be carried out across a broad-range of respiratory areas and, in contrast to other medical research databases (e.g. the Clinical Practice Research Datalink [CPRD]) OPC data offer the additional dimension of patient reported outcomes[42].

6 Study variables and study outcomes

6.1 Primary outcomes

The primary outcome will be a measure of the adjusted proportions of 'no exacerbations[e]' (as defined by the American Thoracic Society/European Respiratory Society (ATS/ERS) Joint Task Force) in the FP/FOR and FP/SAL groups. If the non-inferiority criteria is met a further analysis will be performed to compare the number of exacerbations experienced between the two treatment groups.

6.2 Secondary outcomes

Secondary outcomes will compare the following between FP/FOR and FP/SAL groups. Treatment groups will be further divided into smoking status (smoking, non-smoking, ex-smokers, unknown) and into GINA treatment stages[3] to characterise effectiveness in asthma populations that have more severe disease.

See Section 14.1 for full definitions of abbreviations.

1. Proportion of patients with frequent exacerbations defined as ≥2 exacerbations based on the ATS/ERS Position Statement.

2. Acute respiratory events

3. Risk Domain Asthma Control (RDAC)

4. Overall Asthma Control (OAC)

5. Treatment stability

6. Medication adherence rate

7. Lower-respiratory 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 Consultation**[c];
- **Definite + Probable**: Hospitalisations occurring within a 14-day window (either side of the hospitalisation date) of a lower respiratory read code

8. ICS use – mean daily ICS dose: total ICS dose collected over the outcome year (based on prescription refills) divided by 365 days. This will provide insight into the dosage of ICS, which has been associated with exacerbation rates in patients with asthma treated with combination ICS/LABA inhalers[11].

9. Short-acting beta$_2$ agonist (SABA) use – mean daily SABA dose: total SABA dose collected over the outcome year (based on prescription refills) divided by 365 days.

10. Categorised incidence of oral thrush as defined by topical oral prescriptions to treat oral thrush or Read coded for oral candidiasis

6.3 Cost impact outcomes

1. Total respiratory drug costs[d] ± FDC ICS/LABA drug costs[e]

2. Cost of lower respiratory-related resource utilisation: including combined primary care consultations, A&E attendance and hospital admissions with an asthma or LRTI Read code.

[c] **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) Asthma monitoring
d) Any additional respiratory examinations, referrals, chest x-rays or events

[d] Respiratory drug costs defined as prescription costs for adrenoreceptor agonists, antimuscarinic bronchodilators, compound bronchodilator preparations, theophylline, nebulisers, corticosteroids, cromoglicate and nedocromil, leukotriene receptor antagonists, and antibiotics for lower respiratory tract infections.

[e] Drug costs based on cost of patient prescriptions based on the NHS Dictionary of Medicine and Devices database[37] where brand of prescription item on patient prescription is documented. Where the brand name of prescription item is not available, the generic price is used. The number of drug packs per patient is used where available, else a weighted average of medications is imputed where data is unavailable

6.4 Demographic and baseline variables

Demographic variables

Refer to Section 14.1 for full definitions

a) Age is calculated in years at the index date
b) Sex as the documented gender on the patient record
c) Smoking status as defined as the non-smoker, ex-smoker, current smoker or unknown dependent on status as declared nearest index date
d) Comorbidities including the following comorbidities:
    - Rhinitis – includes patients with diagnostic codes for chronic and allergic rhinitis as well as prescriptions for nasal steroids 1 year during the baseline period.
    - Gastrointestinal Esophageal Reflux Disease (GERD) includes patients with diagnostic codes for GERD or prescriptions for GERD during the baseline period
    - Ischaemic heart disease includes patients with diagnostic codes for ischaemic heart disease during the baseline period
    - Heart failure – includes patients with diagnostic codes for heart failure in the baseline period
    - Hypertension – includes patients with diagnostic codes for hypertension in the baseline period
    - Eczema – includes patients with diagnostic codes for eczema in the baseline period
    - Osteoporosis – includes patients with diagnostic codes for osteoporosis during the baseline period
    - Chronic Kidney Disease – includes patients with diagnostic codes for Chronic Kidney Disease including CKD stage 1 with proteinuria and CKD stages 2-4 during baseline period
    - Anxiety/depression – includes patients with diagnostic codes anxiety and/or depression during the baseline period
    - Diabetes Mellitus – includes patients with diagnostic codes for diabetes mellitus and/or anti-diabetic drug prescriptions including biguanide, sulphonylurea, alpha glucosidase, prandial glucose regulator, thiazolidinedione, GLP-1 analogue, DPP-4 inhibitor, pioglitazone and metformin, rosiglitazone and metformin, and insulin

- CCI score, calculated for the baseline period: a weighted index that takes into account the number and seriousness of comorbid diseases to estimate the risk of death; categorized as 0, 1-4, 5-9 and ≥10[f]

e) Drug history: Including the presence ≥1 of the following prescriptions in the baseline year according to the definition in the British National Formulary[43] for the following categories:
   - Beta-blockers
   - Non-steroidal anti-inflammatory drugs (NSAIDs)
   - Paracetamol

f) Asthma medication dosage, including:
   - ICS dose at index date
   - SABA daily dose

g) Body Mass Index

h) Percent Predicted Peak Flow

i) Total Pack Days (sum (Number days per pack))

j) Refill Rate

k) Allergy prescriptions

l) Respiratory prescriptions

Refer to Appendix 14.2 for mock tables of demographic and baseline variables.

7 Statistical analysis

7.1 Software used and power calculation

Analyses will be carried out using IBM SPSS Statistics Version 22[46], SAS Version 9.3[47] and R 3.1.2[48].

- For the primary outcome, using the proportion of FP/SAL having 'no exacerbation' as 0.758, the expected difference in proportions of 'no exacerbations' between FP/SAL and FP/FOR is 0.033[20].

[f] Updated and adjusted for changes in mortality linked to comorbid conditions. Comorbidity weights taken from Understanding HSMRs: A Toolkit on Hospital Standardised Mortality Ratios, version 9; July 2014; available at http://www.drfoster.com/dr-foster-learning-labs-modules

- Based on non-inferiority limits of -0.035 (-3.5%) for the lower confidence limit using one sided test (alpha=2.5%) of equivalent (non-inferiority) 511 FP/FOR and 2044 FP/SAL patients will be required.
- This will provide 90% power to reject the null hypothesis that FP/SAL and FP/FOR are not equivalent (in favour of the alternative hypothesis that FP/SAL and FP/FOR are equivalent).

7.2 Significance testing

Statistically significant results are defined as $p<0.05$ and p-trend as $0.05 \leq p \leq 0.10$.

7.3 Plots

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

- Frequency plots
- Box and whisker

Frequency plots will illustrate the distribution of the variable and whether categorisation may be necessary (if data is heavily skewed). Box plots will provide a representation of the distribution and identify potential outliers. Plots by treatment groups will highlight differences between groups.

For categorical variables, mosaic plots will illustrate distributions and highlight baseline and outcome differences between treatment groups.

7.4 Matching

Matching will be performed to provide a more robust analysis with matching criteria selected as appropriate and informed by cohort characterisation by analysis of a combination of categorical and continuous demographic and clinical variables. Any residual differences remaining after matching that are considered to be significant between the treatment arms, or predictive of outcomes, will be considered as potential confounders and will be adjusted for through conditional regression modelling.

Patients will be matched on key demographic and disease severity characteristics. The exact matching criteria will be defined following baseline cohort characterisation, but are expected to be:

(i) Age

(ii) Gender

(iii) Short-acting beta agonist use (SABA) – mean daily dose

(iv) Number of oral corticosteroid courses (e.g. 0, 1 , ≥2)

(v) Baseline ICS dose (either last prescribed or mean daily)

(vi) Number of asthma consultations not resulting in an oral corticosteroid course (e.g. 0, 1, ≥2)

(vii) Date of initial prescription ± 3 months

(viii) Smoking history

(ix) GINA treatment category[3]

Each FP/FOR patient will be matched against 4 FP/SAL patients to increase the power of the study.

7.5 Analysis of study outcomes

7.5.1 Test for non-inferiority of FP/FOR vs FP/SAL in exacerbation prevention

See section 14.1 for full definitions

The proportion in the FP/FOR groups with no exacerbations in the outcome period, as defined by ATS/ERS Task Force, will be compared to matched FP/SAL patients using conditional logistic regression. To show non-inferiority, the difference (and 95% confidence interval) in the adjusted proportions between the two treatment groups recording no exacerbations will be calculated. Non-inferiority will be achieved if the proportion of FP/FOR patients calculated to have no exacerbations is no more than 3.5% lower than the proportion of FP/SAL patients calculated to have no exacerbations, i.e. the lower CI of the 95% confidence interval of the difference in proportions is -3.5% or greater. This study provides 90% power to reject the null hypothesis that FP/SAL and FP/FOR are not equivalent in terms of ‘no exacerbations.’

If non-inferiority is met, the total number of serious exacerbations in the outcome period will be compared between treatment groups using a conditional Poisson regression model to obtain an estimate of relative exacerbation rates. The model will use empirical standard errors with adjustments for potential baseline confounders.

7.5.2 Secondary Effectiveness Outcomes

- **Proportion of patients with frequent exacerbations**

The odds ratios between the FP/FOR and FP/SAL patients with ≥2 exacerbations as defined by the ATS/ERS position statement will be compared. Taking the proportion of patients taking FP/SAL as having frequent exacerbations (≥2 exacerbations) as 0.052, the expected difference in proportions of ≥2 exacerbations is 0.033, a two group continuity corrected chi-square test with a 0.05 significance level has an 80% power of rejecting equivalency of the two treatments.

- **Risk domain asthma control**

The adjusted odds of achieving risk domain asthma control will be compared between matched treatment groups using conditional binary logistic regression models. Asthma control status will be used as the dependent variable with treatment and potential confounding factors as explanatory variables.

- **Acute respiratory event rate**

The total number of acute respiratory events in the outcome period will be compared between treatment groups using a conditional Poisson regression model to obtain an estimate of relative respiratory events. The model will use empirical standard errors with adjustments for potential baseline confounders.

- **Overall asthma control**

The adjusted odds of achieving overall asthma control will be compared between matched treatment groups using conditional binary logistic regression models. Asthma control status will be used as the dependent variable with treatment and potential confounding factors as explanatory variables.

- **Medication possession category**

The proportion of patients in medication possession categories will be compared between matched treatment groups.

- **Treatment stability**

The adjusted odds of achieving treatment stability will be compared between matched treatment groups using conditional binary logistic regression models. Treatment stability will be used as the dependent variable with treatment and potential confounding factors as explanatory variables.

- **Hospitalisations**

Where event numbers are sufficient, the total number of hospitalisations in the outcome period will be compared between treatment groups using a conditional Poisson regression model to obtain an estimate of relative hospitalisation rates. The model will use empirical standard errors and adjustments will be made for potential baseline confounders.

- **Adherence**

The proportion of patients in a higher adherence category will be compared between matched treatment groups.

- **SABA usage**

The adjusted odds of being in a higher SABA usage category will be compared between matched treatment groups using conditional ordinal logistic regressional models. The SABA category will be used as the dependent variable with treatment and potential confounding factors as explanatory variables.

- **ICS usage**

The proportion of patients in a higher ICS usage category will be compared between matched treatment groups.

- **Controller/reliever ratio**

The proportion of patients in a higher controller/reliever ratio usage category will be compared between matched treatment groups.

- **Oral Thrush incidence**

The proportion of patients in oral thrush incidence categories will be compared between matched treatment groups.

Summary statistics will be produced for all baseline and outcome variables for each treatment group. For variables that are discrete or continuous numeric variables, the following will be analysed:

- Sample size (n)
- Percentage non missing
- Mean
- Variance/Standard Deviation
- Range (Minimum/Maximum)
- Median
- Inter-quartile Range (25th and 75th percentile)

For categorical variables, summary statistics will include:

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

Any differences will be quantified using unadjusted conditional logistic regression models. Subsets of asthmatics as classified by GINA[3] stages III, IV and IV and smoking/ex-smoker/non-smokers will also be compared as part of the secondary outcomes.

7.6 Confounding factors

Prior research into respiratory disease has identified a range of potential confounders that may affect study outcomes[49]. These include a range of demographic, disease severity, treatment and co-morbid factors. Variables that are shown to be significantly differently or which show a trend towards a difference ($p<0.10$) between the treatment groups at baseline will be considered as potential confounding factors. Outcome analyses will take these findings into account and select appropriate statistical methods to minimise potential confounding. These variables will be extracted where available for all patients, and adjustment for covariates will be done via fitting a regression model for the outcome.

7.6.1 Potential confounders examined at the relevant index date:

- Age

- Gender
- Height
- Weight
- Body Mass Index
- Lung function in terms of percent predicted Peak Expiratory Flow prior to index date
- Smoking status
- ICS or ICS/LABA device type
- ICS drug

7.6.2 Potential confounders examined in the year prior to the index date:

- Presence/absence of comorbid rhinitis
- Use of nasal steroids in the presence of rhinitis
- Presence/absence of comorbid eczema
- Unrelated co-morbidities characterised by Charlson Comorbidity Index (CCI)
- Presence of GERD
- Presence of cardiac disease
- Number of asthma consultations that did not result in a prescription for oral steroid
- 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 where the reason for prescription is LRTI
- Other medications that might interfere with asthma control including beta blockers.
- Number of paracetamol prescriptions in prior year
- Number of NSAIDs prescribed in the prior year
- Number of beta blocker prescriptions in prior year
- 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 GP consultations for asthma that did not result in asthma exacerbations treatment and/or other respiratory illnesses treated with antibiotics in prior year

- Number of hospital outpatient attendances in prior year where asthma and/or other respiratory illness was the reason for referral
- Number of hospitalisations for asthma and/or respiratory illness in the prior year (including non-specific hospitalisations with an asthma/respiratory code within a one week window)
- Number of prescriptions for any antibiotic in the prior year where the reason for the prescription is lower respiratory infection
- Number of short acting $beta_2$ agonist (SABA) prescriptions received in the prior year (calculated based on total combined dose of refilled prescriptions and averaged over 365 days)
- Average ICS daily dose during the prior year (calculated based on total combined dose of refilled prescriptions and averaged over 365 days)
- ICS dose prescribed at index date
- Spacer use/prescription
- First or subsequent change (i.e. ≥second change) change of ICS/LABA drug
- First or subsequent step up (i.e. ≥second change) from ICS to ICS/LABA dose

7.7 Cost Impact Analysis

7.7.1 Outline

Two analyses will be presented:

- A descriptive and comparative analysis of the costs of the treatments during the outcome period

7.7.2 Descriptive Analysis

The following lower respiratory related healthcare costs will be calculated for each treatment group for the outcome period:

- Lower respiratory drug costs (drugs prescribed in any of BNF Sections: 3.1, 3.2 or 3.3 including adrenoreceptor agonists, SABA bronchodilators, antimuscarinic bronchodilators, SABA and compound bronchodilator preparations, theophylline, nebulisers, corticosteroids, cromoglicate and nedocromil, leukotriene receptor antagonists, and antibiotics for lower respiratory tract infections); summarised as
    - Lower respiratory related drug costs (including ICS/FDC)

- Lower respiratory related drug costs (excluding ICS/FDC)

- Lower respiratory related resource utilisation including;
  - Lower respiratory related Read coded primary care consultation[g] costs
  - Lower respiratory related Read coded in patient hospitalisation[h] costs
  - Lower respiratory related Read coded outpatient hospitalisation costs
  - Lower respiratory related Read coded accident and emergency hospitalisation costs

Summary costs will be compared between matched treatment groups using conditional logistic regression.

Further sub-cohort analyses (for example, those based on baseline costs or asthma control status) may also be included as appropriate. For example, results will be compared for controlled and uncontrolled asthmatic patients within treatment groups.

7.7.3 Calculations

- Drug costs =∑ (unit cost multiplied by number of units per year)

- Primary Care Consultation costs = ∑ (unit cost multiplied by number consultations per year)

- Hospital costs = ∑ (unit cost multiplied by number hospital visits per year)

8 Regulatory and ethical compliance

This study was designed and shall be implemented and reported in accordance with the criteria of the “European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study” and follows the ENCePP Code of Conduct (EMA 2014). Once a final version of the protocol has been agreed and reviewed by the advisory group, this study will be registered with www.encepp.eu.

[g] Primary care consultations with a Read code for asthma or LRTI. All primary care consultations considered as GP consultations unless they feature an annual review, in which case they are coded as a nurse consultation

[h] Hospitalisations as defined in Section 14.1

9 Data dissemination

The initial results will aim to be presented in poster format at appropriate thoracic conferences. At least one manuscript containing more detailed results and methodology will be submitted to a journal specialising in respiratory medicine. Submission for publications will aim to be made as soon as the analyses are completed and the results are verified (see the Timelines section of the protocol for anticipated publication dates). Preferred respiratory congresses and journals will be agreed in discussion with Napp Pharmaceuticals, as the study sponsor.

10 Steering Committee Group

The steering committee listed below will provide expert advice into the design of the study.

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11 Research team

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12 Timelines

Action	Expected Timeline (deadlines)
Protocol final definition	26 June 2015
Data extraction	30 June 2015
Matched baseline analysis (stage I)	14 July 2015
Baseline report writing	30 July 2015
Outcome analysis (stage II)	30 August 2015
Final report writing	30 October 2015
First draft of paper	14 December 2015

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14 APPENDIX

14.1 Appendix 1: Definitions

14.1.1 Exacerbation definition based on the ATS/ERS Task Force Position Statement

An exacerbation is defined as an occurrence[i] of the following:

1. Asthma-related[j]:
   a. Hospital admissions OR b. A&E attendance; OR
2. An acute[k] course of oral steroids.

14.1.2 Exacerbation definition based on the ATS/ERS Position Statement – sensitivity definition

An exacerbation is defined as an occurrence[i] of the following:

1. Asthma-related[j]:
   a. Hospital admissions OR b. A&E attendance; OR
2. An acute[k] course of oral corticosteroids with lower respiratory consultation[l].

14.1.3 Acute respiratory event

An acute respiratory event is defined as an occurrence[s] of the following:

1. Asthma-related[j]:
   a. Hospital admissions OR b. A&E attendance; OR
2. An acute[k] course of oral corticosteroids; OR
3. Antibiotics prescribed with lower respiratory consultation [l]

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[i] Where ≥1 oral corticosteroid 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).

[j] **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; (a) – (c) only and excluding where the only lower respiratory code recorded on that day was for a lung function test).

[k] 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 due to prescription strength or frequency of prescriptions.

where “maintenance therapy” is defined as: daily dosing instructions of <=10mg Prednisolone or prescriptions for 1mg or 2.5mg Prednisolone tablets where daily dosing instructions are not available.

[l] **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
d) Any additional respiratory examinations, referrals, chest x-rays or events.

14.1.4 Acute respiratory event - sensitivity definition

An acute respiratory event is defined as an occurrence[s] of the following:

1. Asthma-related[m]:
    a. Hospital admissions OR b. A&E attendance; OR
2. An acute[n] course of oral corticosteroids with lower respiratory consultation[l]; OR
3. Antibiotics prescribed with lower respiratory consultation[l].

14.1.5 Asthma Control Measures

14.1.5.1 Risk-Domain Asthma Control (RDAC)

Controlled: absence of the following:

1. Asthma-related[m]:
    a. Hospital admission AND b. A&E attendance, AND c. out-patient department attendance; AND
2. Acute[n] use of oral corticosteroids; AND
3. Antibiotics prescribed with lower respiratory consultation[l].

Uncontrolled: all others.

14.1.5.2 Risk-Domain Asthma Control (RDAC) – sensitivity definition

Controlled: absence of the following:

1. Asthma-related[m]:
    a. Hospital admission AND b. A&E attendance, AND c.Out-patient department attendance; AND
2. Acute[n] use of oral corticosteroids with lower respiratory consultation[o]; AND

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[m] **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[y]** (see below; (a) – (c) only and excluding where the only lower respiratory code recorded on that day was for a lung function test).

[n] Acute oral corticosteroid 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 due to prescription strength or frequency of prescriptions

[o] **Lower Respiratory Consultations -** consist of the following:

3. Antibiotics prescribed with lower respiratory consultation[o].

Uncontrolled: all others.

14.1.5.3 Overall Asthma Control (OAC) – Risk and Impairment

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.

14.1.6 Treatment Stability

Excluding changes in therapeutic regimen that are likely to be motivated by cost-savings.

Stable:

1. Achieved Risk Domain Asthma Control (as defined above); AND

2. No additional therapy defined as no:
   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.

14.1.6.1 Treatment stability (sensitivity definition)

Stable:

1. Achieved Risk Domain Asthma Control (as defined above); AND

2. No additional or change in therapy defined as no:
   a. Increased dose of ICS (≥50% increase of that prescribed at index date) AND/OR
   b. Change in ICS AND/OR
   c. Change in delivery device AND/OR
   d. Use of additional therapy as defined by: long-acting bronchodilator (LABA), theophylline, leukotriene receptor antagonists (LTRAs).

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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;
d) Any additional respiratory examinations, referrals, chest x-rays or events.

Unstable: all others.

14.1.7 Reliever Usage

14.1.7.1 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);

i.e. $\frac{Number\ of\ inhalers * doses\ per\ inhaler}{365} * strength$

and categorised as appropriate to the data.

14.1.7.2 Controller-to-Reliever Ratio

Please note that when inhaler duration is very different and not comparable between two treatment groups, the number of controller units – and so Controller to Reliever Ratio - is a biased outcome and results are not meaningful.

Controllers are defined as ICS (including fixed combination ICS/LABA) and LTRA, while relievers are SABA. For ICS or ICS/LABA and for SABA, one unit is taken to be one inhaler; for LTRA one unit is one prescription.

Controllers: ICS (including fixed combination ICS/LABA) and LTRA. For ICS a unit is taken to be one inhaler; for LTRA a unit is one prescription.

Relievers: SABA, with a unit taken to be one inhaler.

Note: LABA is not included as a controller (as the number of "controllers" maybe distorted by fixed combination /separate inhalers).

The ratio is usually categorised as a dichotomous variable: < 0.5 (low) and ≥ 0.5 (high). A higher Controller-to-Reliever ratio (≥ 0.5) has been proven to be significantly related to improved asthma-related quality of life, better disease control and reduced symptoms.

14.1.8 Adherence to Therapy

Please note that when inhaler duration is very different and not comparable between two treatment groups, adherence is a biased outcome and results are not meaningful. Adherence to therapy should always be an "Explanatory" outcome rather than a primary / secondary outcome.

14.1.8.1 Adherence over 1 year

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

Total Pack Days = Σ (Number days per pack)

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

14.1.8.2 Adherence over part year

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

Total Pack Days = Σ (Number of days per pack)

Number of Prescription Days = (date of last script – date of first script) + Number pack days of last script

Refill Rate % = (Total pack days / Number prescription days) x 100

14.1.8.3 Medication Possession Ratio (MPR)

MPR is usually categorised as a dichotomous variable: <80% (non-adherent) and ≥80% (adherent).

14.1.9 Hospitalisations

A lower-respiratory related 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 Consultation**[p]
- **Definite + Probable**: Hospitalisations occurring within a 7-day window (either side of the hospitalisation date) of a lower respiratory read code

14.1.10 Cost impact outcomes

a) **Respiratory drug costs ± FDC ICS/LABA drug costs:** prescription costs for adrenoreceptor agonists, SABA bronchodilators, SABA bronchodilator preparations, theophylline, nebulisers, corticosteroids, cromoglicate and nedocromil, leukotriene receptor antagonists, and antibiotics for lower respiratory tract infections

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[p]**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) Asthma monitoring.
d) Any additional respiratory examinations, referrals, chest x-rays or events.

b) Cost of respiratory related resource utilisation: combined and disaggregated primary care consultations, A&E attendance, Out Patient Department attendance, hospital admission coded for asthma or a lower respiratory Read code

14.1.10.1 Primary Care Consultations Costs

All primary care consultations are considered to be GP consultations unless marked by a Quality and Outcomes Framework annual review where it will be considered as a nurse consultation, or is specifically marked as a nurse consultation.

14.1.10.2 Secondary Care Costs

A&E attendance – emergency non-admitted care with or without the use of an ambulance.

Inpatient – planned or unplanned admission (long or short stay) and including an emergency requiring ≥1 overnight stay.

Outpatient – Non emergency planned visit without admission.

14.1.11 Age

Defined as calculated in years at the initial prescription date.

14.1.12 Sex

Defined the documented gender on the patient record

14.1.13 Smoking status

Defined as the non-smoker, ex-smoker or current smoker dependent on status as declared on primary care records.

14.1.14 Drug History

Including the presence of the following drugs:

14.1.14.1 Beta blockers

As defined as ≥1 prescription for beta blockers listed in the British National Formulary during the outcome or baseline period

14.1.14.2 NSAIDs

As defined as ≥1 prescription for NSAIDs in section in the British National Formulary during the outcome or baseline period

14.1.14.3 Paracetamol

Defined as ≥1 prescription for paracetamol in the outcome or baseline period

14.1.15 Asthma medication dosage

14.1.15.1 ICS dose at initial prescription

As defined as corticosteroid dose in µg as calculated by the total corticosteroid content of the inhaler by the actual prescriptions per month

14.1.15.2 SABA daily dose

As defined as short acting beta agonist dosage as calculated by the salbutamol dosage multiplied by the number of prescriptions per month for SABA multiplied by total SABA dose in a pack (10,000 µg for Salbutamol CFC free)/30 days

14.1.16 Body Mass Index

The **Body Mass Index** is a representative measure of body weight based on the weight and height of the subject. It is defined as the weight (in kg) divided by the square of the height (in m) and is measured in kg/m^2.

14.1.17 Percent Predicted Peak Expiratory Flow

The percent predicted Peak Expiratory Flow (PEF) values have been calculated using the following predicted values derived from Roberts' equations (for patients aged ≥19 years at PF reading) and Rosenthal's equations (for patients aged <19 years at PF reading):

For male patients aged ≥19 years (Roberts):

Predicted PEF (litres/sec) = (5.317 x *[height in metres]) - (0.062* x *[age in yrs]) + 3.884*

For female patients aged ≥19 years (Roberts):

Predicted PEF (litres/sec) = (4.087 x *[height in metres]) - (0.050* x *[age in yrs]) + 2.945*

For male patients aged 4-18 years and < 162.6 cm tall (Rosenthal):

Predicted PEF (litres/sec) = (0.073 x *[height in cm]) - 5.98*

For male patients aged 4-18 years and ≥ 162.6 cm tall (Rosenthal):

Predicted PEF (litres/sec) = (0.125 x *[height in cm]) - 13.14*

For female patients aged 4-18 years and < 152.6 cm tall (Rosenthal):

Predicted PEF (litres/sec = (0.079 x *[height in cm]) - 6.79*

For female patients aged 4-18 years and ≥ 152.6 cm tall (Rosenthal):

Predicted PEF (litres/sec) = (0.064 x *[height in cm]) - 3.94*

Total Pack Days = Σ (Number days per pack)

Refill Rate **%** = x 100

14.1.18 Allergy Prescriptions

Any drugs prescribed in any of British National Formulary (BNF) Sections 3.4.1, 3.4.2, 3.4.3, 3.7, 3.8, 3.8, 3.9.1, 3.9.2, 3.10, 12.2.1, 12.2.2, 13.2.1, 13.2.2, 13.4, 13.5.1.

14.1.19 Respiratory Prescriptions

Any drugs prescribed in any of BNF Sections: 3.1, 3.2 or 3.3 including adrenoreceptor agonists, antimuscarinic bronchodilators, compound bronchodilator preparations,

theophylline, nebulisers, corticosteroids, cromoglicate, nedocromil, leukotriene receptor antagonists.

14.1.20 Cost impact data

Cost impact data covers a description and comparative analysis of the costs of treatment during the outcome period. This covers medication, primary care costs, and secondary costs as defined below:

14.1.20.1 Medication

- NHS DM+D[37] is the primary source of all drug and device costs, with the British National Formulary (BNF)[43] and the Medical Index of Medicinal Substances[50] (MIMS) to be utilised to fill any gaps
- Where a specific brand of product cannot be determined from a prescription, the price of the generic product is applied
- Where the number of respiratory inhalers prescribed on a given prescription cannot be determined, it is assigned the average number prescribed for that class of inhaler, based on information available in the OPCRD[42] database
- Where the pack size of a maintenance medication (respiratory and non-respiratory) on a given prescription cannot be determined, it will be assigned to the average number prescribed for that class of medication, based on information available in the OPCRD database[42].
- Where the pack size of an acute medication (respiratory and non-respiratory) on a given prescription cannot be determined, it will be assigned to the average number prescribed for that class of acute medication, based on information available in the OPCRD database[42].

14.1.20.2 Primary care costs

- Primary care consultation Read codes are priced as GP consultation costs or nurse consultation costs, as appropriate
    - In the event that this cannot be determined a GP consultation cost should be applied
- Prices assigned to primary care consultation costs is taken from the latest PSSRU 2014 document[44] –found on pages 192 and 195 of the current version

- GP 11.7 minute consultation (with qualification costs[q] and including direct care staff costs[r]) **£46**
- Nurse 15.5 minute consultation (with qualification costs , priced as per hour of face-to-face contact at £53) **£13.69**

- Prices are likely to be an over-estimate and can only be compared as a relative cost, not a real cost

14.1.20.3 Secondary care costs

- Prices based on the current PSSRU document[44] (page 111 of the 2014 version) when considering average costs that are not condition-specific (ie not just respiratory-related costs)
- Prices based on the latest NHS reference costs[45] (2013-2014) when investigating respiratory-related costs[s]

- Definitions
  - A&E attendance – Emergency non-admitted care with or without the use of an ambulance
  - Inpatient – Planned or unplanned admission (long or short stay) and including an emergency requiring ≥1 overnight stay
  - Outpatient – Non emergency planned visit without admission

[q] Investment cost of education – justified by statement at the top of page 268 of the same document[44]: 'The investment costs of education should be included when evaluating the cost-effectiveness of different approached to using health service staff so that all the costs implicit in changing the professional mix are considered'

[r] Direct care staff (from page 194 of current PSSRU[44]): 'Each full time equivalent (FTE) practitioner (excluding GP registrars and GP retainers) employed 0.47 FTE practice nurse (includes salary and on costs)'

[s] The NHS reference costs allow the pricing to be more accurate, when focusing on respiratory-related costs

- Current (2014) PSSRU[44] general hospital costs are as follows:
    - A&E attendance £223[t]
    - Inpatient attendance £611[u]
    - Outpatient attendance £109[v]

- Respiratory-specific costs from the National Schedule Reference Costs (2013-2014) are as follows:
    - A&E attendance £171.44
    - Inpatient (asthma) £584.25; Inpatient (COPD) £711.06
    - Outpatient £150.00

- Prices are relative costs not real costs, due to the definitions of the categories given above and the assumptions associated with them

- Hospital admission Read codes that fall within 14 days of other hospital admission Read codes will not be counted as a separate admission to avoid double counting

14.2 Appendix 2: Mock baseline results tables

14.2.1 1. Demographics

Table 2: Mock table for demographics

[t] This is the Ambulance Service 'See, treat and convey' cost from PSSRU 2014[44]

[u] As non-elective with a short-stay, considered the most common occurrence

[v] Weighted average of all outpatient attendances from PSSRU[44]

		Treatment Group		TOTAL	p-value*
		FP/SAL (MDI)	FP/FOR		
Age at IPD - (years)	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	0.856
	Mean (SD)	53.37 (14.73)	53.40 (14.88)	53.37 (14.76)	
	Median (IQR)	53 (43, 65)	54 (43, 65)	54 (43, 65)	
Height (m) – closest to IPD	N (% non-missing)	1124 (98.1)	379 (99.2)	1503 (98.4)	0.626
	Mean (SD)	1.68 (0.10)	1.68 (0.10)	1.68 (0.10)	
	Median (IQR)	1.68 (1.60, 1.75)	1.68 (1.60, 1.75)	1.68 (1.60, 1.75)	
Weight (kg) – closest to IPD	N (% non-missing)	1109 (96.8)	376 (98.4)	1485 (97.2)	0.926
	Mean (SD)	81.4 (19.2)	81.8 (19.8)	81.5 (19.6)	
	Median (IQR)	79 (68, 92)	80 (68, 92)	79 (67, 92)	
BMI (kg/m^2)	N (% non-missing)	1106 (96.5)	375 (98.2)	1481 (96.9)	0.977
	Mean (SD)	28.9 (6.1)	28.9 (6.9)	28.9 (6.3)	
	Median (IQR)	27.9 (24.7, 32.2)	27.6 (24.1, 32.1)	27.8 (24.6, 32.2)	
Percent Predicted Peak Flow readings (%)	N (% non-missing)	1000 (87.3)	314 (82.2)	1314 (86.0)	0.426
	Mean (SD)	82.93 (18.61)	81.96 (18.58)	82.70 (18.60)	
	Median (IQR)	84.3 (70.8, 95.8)	83.9 (69.7, 94.8)	84.3 (70.8, 95.5)	

Figure 3: Mock table for categorised age groups

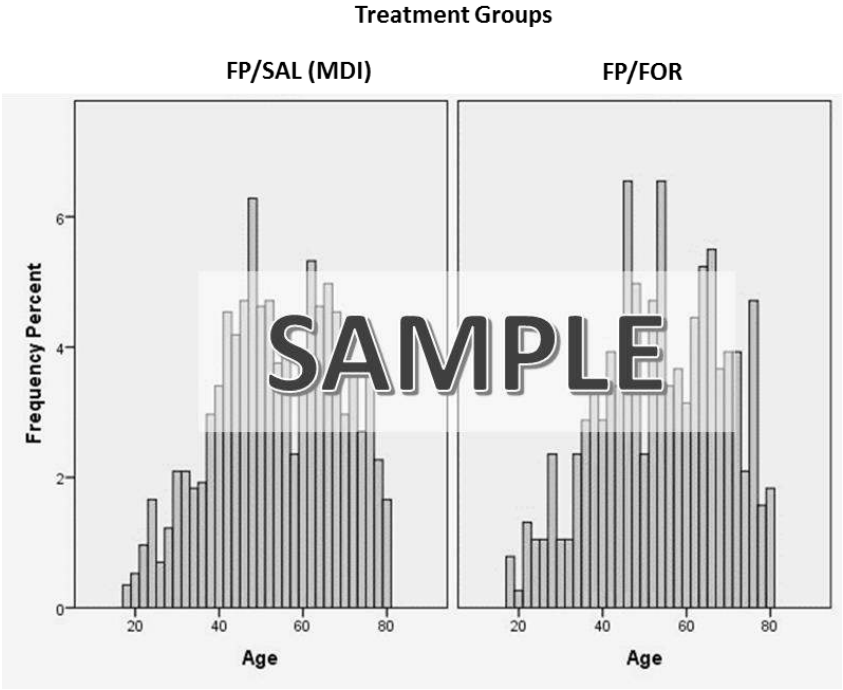

Figure 4: Mock table for categorised peak flow

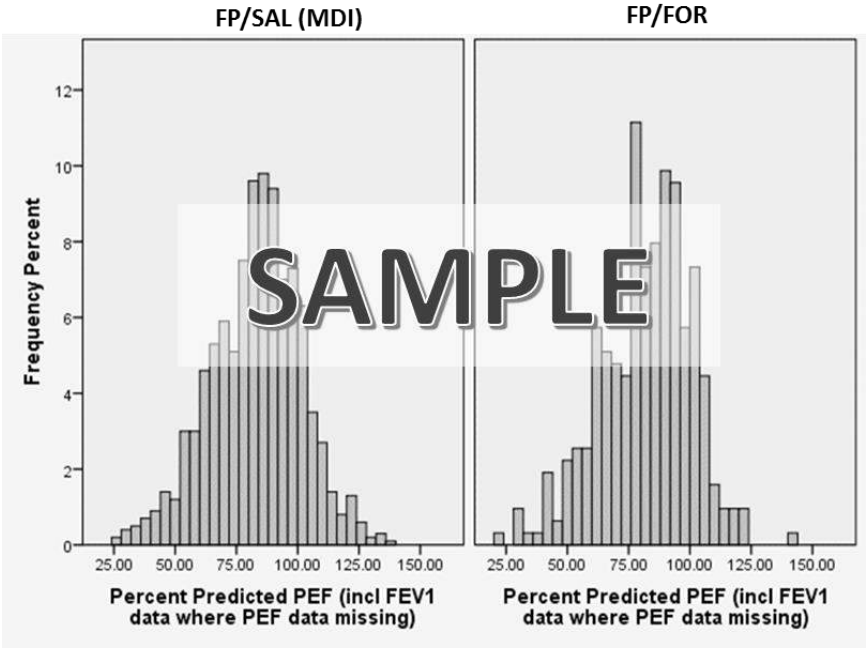

Table 3:Mock table for demographics

		Treatment Group		TOTAL	P value*
		FP/SAL (MDI)	FP/FOR		
Gender	Male n (%)	507 (44.2)	169 (44.2)	676 (44.2)	N/A
	Female n (%)	639 (55.8)	213 (55.8)	852 (55.8)	
	Total n (%)	1146 (100)	382 (100)	1528 (100)	
Age Group in years (categorised)	18-60 n (%)	723 (63.1)	241 (63.1)	964 (63.1)	N/A
	61-80 n (%)	423 (36.9)	141 (36.9)	564 (36.9)	
	Total n (%)	1146 (100)	382 (100)	1528 (100)	
BMI (categorised)	Underweight (n) (%)	9 (0.8)	5 (1.3)	14 (0.9)	0.114
	Normal (n) (%)	297 (26.9)	109 (28.5)	406 (27.9)	
	Overweight (n) (%)	400 (36.2)	130 (34.0)	530 (35.8)	
	Obese (n) (%)	400 (36.2)	124 (32.1)	524 (35.4)	
	Total n (%)	1106 (100)	375 (100)	1481 (100)	
Smoking Status	Non Smokers n (%)	594 (51.8)	198 (51.8)	792 (51.8)	N/A
	Current Smokers n (%)	210 (18.3)	70 (18.3)	280 (18.3)	
	Ex-Smokers n (%)	342 (29.8)	114 (29.8)	456 (29.8)	
	Total n (%)	1146 (100)	382 (100)	1528 (100)	

Table 4:Mock table for exacerbations

		Treatment Group		TOTAL	P value*
		FP/SAL (MDI)	FP/FOR		
Exacerbations (ATS definition)	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	0.112
	Mean (SD)	0.29 (0.76)	0.34 (1.13)	0.31 (0.87)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
Exacerbations (Clinical Definition)	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	0.286
	Mean (SD)	0.51 (0.94)	0.55 (1.26)	0.52 (1.03)	
	Median (IQR)	0 (0, 1)	0 (0, 1)	0 (0, 1)	
Acute Oral Steroid Courses	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	0.081
	Mean (SD)	0.29 (0.76)	0.34 (1.13)	0.30 (0.86)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
Acute Oral Steroid Prescriptions	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	0.023
	Mean (SD)	0.30 (0.82)	0.39 (1.28)	0.32 (0.96)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
LRTI Consultations resulting in script for Antibiotics	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	0.729
	Mean (SD)	0.28 (0.65)	0.28 (0.70)	0.28 (0.66)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
Asthma Consultations	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	<0.001
	Mean (SD)	1.43 (1.38)	1.70 (1.44)	1.50 (1.40)	
	Median (IQR)	1 (1, 2)	1 (1, 2)	1 (1, 2)	
Asthma Consultations No Oral Steroids	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	0.003
	Mean (SD)	1.31 (1.29)	1.52 (1.30)	1.36 (1.30)	
	Median (IQR)	1 (1, 2)	1 (1, 2)	1 (1, 2)	
Non Asthma-related Consultations	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	0.613
	Mean (SD)	9.76 (9.12)	10.01 (8.04)	9.82 (8.86)	
	Median (IQR)	7 (4, 13)	8 (4, 14)	8 (4, 13)	
Primary care Consultations	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	0.301
	Mean (SD)	11.18 (9.38)	11.71 (8.27)	11.31 (9.12)	
	Median (IQR)	9 (5, 15)	10 (5, 16)	9 (5, 15)	

* Conditional Logistic Regression

		Treatment Group		TOTAL	P value*
		FP/SAL (MDI)	FP/FOR		
Allergy scripts	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	0.893
	Mean (SD)	3.57 (7.15)	3.51 (7.23)	3.55 (7.16)	
	Median (IQR)	1 (0, 4)	0 (0, 4)	1 (0, 4)	
Respiratory scripts	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	<0.001
	Mean (SD)	11.00 (7.35)	13.24 (8.57)	11.56 (7.73)	
	Median (IQR)	9 (6, 14)	11 (7, 17)	10 (6, 15)	
SABA scripts	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	<0.001
	Mean (SD)	3.75 (3.68)	4.45 (4.58)	3.93 (3.93)	
	Median (IQR)	3 (1, 5)	3 (1, 6)	3 (1, 6)	
SABA Inhalers	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	0.032
	Mean (SD)	5.13 (5.29)	5.42 (6.36)	5.20 (5.58)	
	Median (IQR)	4 (1, 8)	4 (1, 8)	4 (1, 8)	
SABA Dosage (mcg)	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	0.022
	Mean (SD)	279.74 (289.15)	296.38 (348.24)	283.9 (3	
	Median (IQR)	219.2 (54.8, 438.4)	219.2 (54.8, 438	(54.8,	
ICS scripts	N (% non-missing)	1146 (100)	382 (	1528 (	<0.001
	Mean (SD)	6.19 (3.36)	7.50 (	6.52 (3.40)	
	Median (IQR)	5 (4, 8)		6 (4, 9)	
ICS inhalers	N (% non-missing)	1146 (100)		1528 (100)	0.218
	Mean (SD)	8.1 (4.50)	(3.72)	8.20 (4.32)	
	Median (IQR)	8 (	8 (5, 11)	8 (5, 11)	
Average ICS daily dose	N (% non-missing)	1146 (10	382 (100)	1528 (100)	0.253
	Mean (SD)	374.89 (255.23)	387.99 (240.96)	378.16 (251.72)	
	Median (IQR)	328.8 (197.3, 493.2)	328.8 (205.5, 493.2)	328.8 (205.5, 493.2)	
ICS dose prior to IPD (mcg) §	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	N/A
	Mean (SD)	553.27 (223.55)	553.27 (223.74)	553.27 (223.52)	
	Median (IQR)	500 (500, 500)	500 (500, 500)	500 (500, 500)	
ICS dose at IPD[18] (mcg)	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	<0.001
	Mean (SD)	553.27 (223.55)	360.21 (79.95)	505.01 (214.62)	
	Median (IQR)	500 (500, 500)	400 (400, 400)	500 (400, 500)	
Adherence to ICS	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	0.783
	Mean (SD)	81.97 (40.49)	82.55 (34.05)	82.11 (38.97)	
	Median (IQR)	80.2 (54.1, 99.1)	81.4 (56.6, 99.2)	80.6 (54.7, 99.2)	
Medication Possession Ratio	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	0.181
	Mean (SD)	66.09 (26.97)	67.99 (24.98)	66.57 (26.49)	
	Median (IQR)	65.75 (41.10, 95.89)	65.75 (49.32, 90.41)	65.75 (41.10, 93.15)	
Controller to Reliever Ratio	N (% non-missing)	1146 (100)	382 (100)	1528 (100)	0.019
	Mean (SD)	0.68 (0.22)	0.69 (0.21)	0.68 (0.21)	
	Median (IQR)	0.67 (0.50, 0.86)	0.68 (0.50, 0.86)	0.67 (0.50, 0.86)	

* Conditional Logistic Regression

Table 5: Mock table for demographics

14.3 Appendix 3: Mock outcome results tables

See section 14.1 for full definitions of terms.

1. Non-inferiority in terms of patients with 'no severe exacerbations' (ATS/ERS Task Force definition) between FP/FOR and FP/SAL

	Comparison between OR FP/SAL and FP/FOR (n = sample)	
	FP/SAL 95th CI	**FP/FOR** 95th CI
Patients with "No exacerbations" (%) - Asthma-related emergency department (ED) attendance; OR - Asthma related inpatients admissions; OR - Prescription for an acute course of oral corticosteroids from a lower respiratory event	SAMPLE	SAMPLE

Non inferiority met if lower confidence interval for FP/FOR is <0.035 for the lower confidence limit

Table 6: Mock table for primary outcome

1a. Rate of exacerbations between FP/FOR and FP/SAL

	FP/SAL	FP/FOR
Rate of exacerbations		
Unadjusted Rate ratio (95 % CI)	**SAMPLE**	
Adjusted Rate ratio (95 % CI)		

Table 6a: Co-primary outcome of rate ratio

2. Less 'frequent exacerbations' (ATS/ERS Task Force definition) between FP/SAL and FP/FOR

	Comparison between OR FP/SAL and FP/FOR (n = sample)	
	FP/SAL (CI)	**FP/FOR** (CI)
Patients with "≥2 exacerbations" (%) - Asthma-related emergency department (ED) attendance; OR - Asthma related inpatients admissions; OR - Prescription for an acute course of oral corticosteroids from a lower respiratory event	SAMPLE	SAMPLE

Table 7: Mock table for secondary outcome

3. Number of exacerbations (ATS/ERS Task Force definition)

Exacerbations	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	918 (80.1)	309 (80.9)	1227 (80.3)
1 n (%)	155 (13.5)	49 (12.8)	204 (13.4)
2+ n (%)	73 (6.4)	24 (6.3)	97 (6.3)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 8: Mock table for exacerbations

Number of exacerbations (ATS/ERS Task Force definition) in smokers

Exacerbations	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	918 (80.1)	309 (80.9)	1227 (80.3)
1 n (%)	155 (13.5)	49 (12.8)	204 (13.4)
2+ n (%)	73 (6.4)	24 (6.3)	97 (6.3)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 9. Mock table for exacerbations in smokers

Number of exacerbations (ATS/ERS Task Force definition[w]) in ex-smokers

Exacerbations	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	918 (80.1)	309 (80.9)	1227 (80.3)
1 n (%)	155 (13.5)	49 (12.8)	204 (13.4)
2+ n (%)	73 (6.4)	24 (6.3)	97 (6.3)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 10: Mock table for exacerbations in ex-smokers

Number of exacerbations (ATS/ERS Task Force definition[w]) in non-smokers

Exacerbations	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	918 (80.1)	309 (80.9)	1227 (80.3)
1 n (%)	155 (13.5)	49 (12.8)	204 (13.4)
2+ n (%)	73 (6.4)	24 (6.3)	97 (6.3)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 11: Mock table for exacerbations in non-smokers

Number of exacerbations (ATS/ERS Task Force definition) in patients classified as GINA stage III

Exacerbations	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	918 (80.1)	309 (80.9)	1227 (80.3)
1 n (%)	155 (13.5)	49 (12.8)	204 (13.4)
2+ n (%)	73 (6.4)	24 (6.3)	97 (6.3)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 12: Mock table for exacerbations in patients classified as GINA stage III

Number of exacerbations (ATS/ERS Task Force definition) in patients classified as GINA stage IV and V

Exacerbations	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	918 (80.1)	309 (80.9)	1227 (80.3)
1 n (%)	155 (13.5)		204 (13.4)
2+ n (%)	73 (6.4)	24 (6.3)	97 (6.3)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 13: Mock table for exacerbations in patients classified as GINA stage IV and V

4. Acute respiratory events

Respiratory events	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	918 (80.1)	309 (80.9)	1227 (80.3)
1 n (%)	155 (13.5)		204 (13.4)
2+ n (%)	73 (6.4)	24 (6.3)	97 (6.3)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 14: Mock table for acute respiratory events

Acute respiratory events in smokers

Respiratory events	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	918 (80.1)	309 (80.9)	1227 (80.3)
1 n (%)	155 (13.5)		204 (13.4)
2+ n (%)	73 (6.4)	24 (6.3)	97 (6.3)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 15: Mock table for acute respiratory events in smokers

Acute respiratory events in ex-smokers

Respiratory events	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	918 (80.1)	309 (80.9)	1227 (80.3)
1 n (%)	155 (13.5)		204 (13.4)
2+ n (%)	73 (6.4)	24 (6.3)	97 (6.3)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 16: Mock table for acute respiratory events in ex-smokers

Acute respiratory events in non-smokers

Respiratory events	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	918 (80.1)	309 (80.9)	1227 (80.3)
1 n (%)	155 (13.5)		204 (13.4)
2+ n (%)	73 (6.4)	24 (6.3)	97 (6.3)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 17: Mock table for acute respiratory events in non smokers

Acute respiratory events in patients classified as GINA stage III

Respiratory events	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	918 (80.1)	309 (80.9)	1227 (80.3)
1 n (%)	155 (13.5)	[illegible]	204 (13.4)
2+ n (%)	73 (6.4)	24 (6.3)	97 (6.3)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 18: Mock table for acute respiratory events[y] in patients classified as GINA stage III[3]

Acute respiratory events[y] in patients classified as GINA stage IV and V

Respiratory events	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	918 (80.1)	309 (80.9)	1227 (80.3)
1 n (%)	155 (13.5)	[illegible]	204 (13.4)
2+ n (%)	73 (6.4)	24 (6.3)	97 (6.3)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 19: Mock table for acute respiratory events[y] in patients classified as GINA stage IV and V

5. Risk Domain Asthma Control Status (RDAC status)

Risk Domain Asthma Control Status – IPDC	Treatment Group		Total
	FP/SAL	FP/FOR	
Controlled n (%)	786 (68.6)	277 (72.5)	1063 (69.6)
Uncontrolled n (%)	360 (31.4)	[illegible]	465 (30.4)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders * (95% CI)	1.00	1.15 (0.88, 1.52)	

Table 20: Mock table for risk domain control asthma status

RDAC for smokers

Risk Domain Asthma Control Status – IPDC	Treatment Group		Total
	FP/SAL	FP/FOR	
Controlled n (%)	786 (68.6)	277 (72.5)	1063 (69.6)
Uncontrolled n (%)	360 (31.4)	[illegible]	465 (30.4)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders * (95% CI)	1.00	1.15 (0.88, 1.52)	

Table 21: Mock table for RDAC for smokers

RDAC for ex-smokers

Risk Domain Asthma Control Status – IPDC	Treatment Group		Total
	FP/SAL	FP/FOR	
Controlled n (%)	786 (68.6)	277 (72.5)	1063 (69.6)
Uncontrolled n (%)	360 (31.4)	[illegible]	465 (30.4)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders * (95% CI)	1.00	1.15 (0.88, 1.52)	

Table 22: Mock table for RDAC for ex-smokers

RDAC for non-smokers

Risk Domain Asthma Control Status – IPDC	Treatment Group		Total
	FP/SAL	FP/FOR	
Controlled n (%)	786 (68.6)	277 (72.5)	1063 (69.6)
Uncontrolled n (%)	360 (31.4)	[illegible]	465 (30.4)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders * (95% CI)	1.00	1.15 (0.88, 1.52)	

Table 23: Mock table for RDAC for non smokers

RDAC for patients classified as GINA stage III[3]

Risk Domain Asthma Control Status – IPDC	Treatment Group		Total
	FP/SAL	FP/FOR	
Controlled n (%)	786 (68.6)	277 (72.5)	1063 (69.6)
Uncontrolled n (%)	360 (31.4)	[illegible]	465 (30.4)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders * (95% CI)	1.00	1.15 (0.88, 1.52)	

Table 24: Mock table for RDAC for patients classified as GINA stage III[3]

RDAC for patients classified as GINA stage IV and V[3]

Risk Domain Asthma Control Status – IPDC	Treatment Group		Total
	FP/SAL	FP/FOR	
Controlled n (%)	786 (68.6)	277 (72.5)	1063 (69.6)
Uncontrolled n (%)	360 (31.4)	[illegible]	465 (30.4)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders * (95% CI)	1.00	1.15 (0.88, 1.52)	

Table 25: Mock table for RDAC for patients classified as GINA stage IV and V[3]

5. Overall Asthma Control (OAC) Status (Risk and Impairment)

Overall Asthma Control Status – IPDC	Treatment Group		Total
	FP/SAL	FP/FOR	
Controlled n (%)	358 (31.2)	149 (39.0)	507 (33.2)
Uncontrolled n (%)	788 (68.8)	233 (61.0)	1021 (66.8)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders* (95% CI)	1.00	1.56 (1.14, 2.14)	
Odds Ratio adjusted for baseline confounders* and BMI (categorised) (95% CI)	1.00	1.53 (1.10, 2.11)	

Table 26: Mock table for overall asthma control status

OAC for smokers

Overall Asthma Control Status – IPDC	Treatment Group		Total
	FP/SAL	FP/FOR	
Controlled n (%)	358 (31.2)	149 (39.0)	507 (33.2)
Uncontrolled n (%)	788 (68.8)	233 (61.0)	1021 (66.8)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders* (95% CI)	1.00	1.56 (1.14, 2.14)	
Odds Ratio adjusted for baseline confounders* and BMI (categorised) (95% CI)	1.00	1.53 (1.10, 2.11)	

Table 27: Mock table for OAC for smokers

OAC for ex-smokers

Overall Asthma Control Status – IPDC	Treatment Group		Total
	FP/SAL	FP/FOR	
Controlled n (%)	358 (31.2)	149 (39.0)	507 (33.2)
Uncontrolled n (%)	788 (68.8)	233 (61.0)	1021 (66.8)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders* (95% CI)	1.00	1.56 (1.14, 2.14)	
Odds Ratio adjusted for baseline confounders* and BMI (categorised) (95% CI)	1.00	1.53 (1.10, 2.11)	

Table 28: Mock table for OAC for ex-smokers

OAC for non-smokers

Overall Asthma Control Status – IPDC	Treatment Group		Total
	FP/SAL	*FP/FOR*	
Controlled n (%)	358 (31.2)	149 (39.0)	507 (33.2)
Uncontrolled n (%)	788 (68.8)	233 (61.0)	1021 (66.8)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders* (95% CI)	1.00	1.56 (1.14, 2.14)	
Odds Ratio adjusted for baseline confounders* and BMI (categorised) (95% CI)	1.00	1.53 (1.10, 2.11)	

Table 29: Mock table for OAC for non-smokers

OAC for patients classified as GINA stage III[3]

Overall Asthma Control Status – IPDC	Treatment Group		Total
	FP/SAL	*FP/FOR*	
Controlled n (%)	358 (31.2)	149 (39.0)	507 (33.2)
Uncontrolled n (%)	788 (68.8)	233 (61.0)	1021 (66.8)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders* (95% CI)	1.00	1.56 (1.14, 2.14)	
Odds Ratio adjusted for baseline confounders* and BMI (categorised) (95% CI)	1.00	1.53 (1.10, 2.11)	

Table 30: Mock table for OAC for patients classified as GINA stage III[3]

OAC for patients classified as GINA stage IV and V[3]

Overall Asthma Control Status – IPDC	Treatment Group		Total
	FP/SAL	*FP/FOR*	
Controlled n (%)	358 (31.2)	149 (39.0)	507 (33.2)
Uncontrolled n (%)	788 (68.8)	233 (61.0)	1021 (66.8)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders* (95% CI)	1.00	1.56 (1.14, 2.14)	
Odds Ratio adjusted for baseline confounders* and BMI (categorised) (95% CI)	1.00	1.53 (1.10, 2.11)	

Table 31: Mock table for OAC for patients classified as GINA stage IV and V[3]

6. ICS and SABA Daily Dose Categories

		Comparison between FP/SAL and FP/FOR (n = sample)		p-value *
		(FP/SAL)	(FP/FOR)	
ICS daily dose (µg)	Mean (SD)	1,256.8 (799.1)	1,346.6 (783.9)	0.005**
	Median (IQR)	1,068.5 (658,1808)	1,150.7 (658,2137)	
ICS daily dose (categorised) (µg)	0-450	23 (15.0)	21 (13.7)	0.016†
	451-750	23 (15.0)	26 (17.0)	
	751-1,000	28 (18.3)	18 (11.8)	
	1,001-1,500	29 (19.0)	SAMPLE	
	1,501-2,000	27 (17.6)	19 (12.4)	
SABA daily dose (µg)	Mean (SD)	2.3 (2.2)	2.3 (2)	0.957**
	Median (IQR)	1.9 (1,3)	1.9 (1,3)	
SABA daily dose (categorised) (µg)	0.01-1.00	31 (21.8)	30 (21.1)	0.549†
	1.01-2.00	40 (28.2)	40 (28.2)	
	2.01-3.50	40 (28.2)	37 (26.1)	
	3.51+	31 (21.8)	35 (24.6)	

*Conditional logistic regression

Table 32: Mock table for ICS and SABA dose

ICS and SABA daily doses categories for smokers

		Comparison between FP/SAL and FP/FOR (n = sample)		p-value *
		(FP/SAL)	(FP/FOR)	
ICS daily dose (µg)	Mean (SD)	1,256.8 (799.1)	1,346.6 (783.9)	0.005**
	Median (IQR)	1,068.5 (658,1808)	1,150.7 (658,2137)	
ICS daily dose (categorised) (µg)	0-450	23 (15.0)	21 (13.7)	0.016†
	451-750	23 (15.0)	26 (17.0)	
	751-1,000	28 (18.3)	18 (11.8)	
	1,001-1,500	29 (19.0)	SAMPLE	
	1,501-2,000	27 (17.6)	19 (12.4)	
SABA daily dose (µg)	Mean (SD)	2.3 (2.2)	2.3 (2)	0.957**
	Median (IQR)	1.9 (1,3)	1.9 (1,3)	
SABA daily dose (categorised) (µg)	0.01-1.00	31 (21.8)	30 (21.1)	0.549†
	1.01-2.00	40 (28.2)	40 (28.2)	
	2.01-3.50	40 (28.2)	37 (26.1)	
	3.51+	31 (21.8)	35 (24.6)	

Table 33: Mock table for ICS and SABA dose for smokers

ICS and SABA dose categories for ex-smokers

		Comparison between FP/SAL and FP/FOR (n = sample)		p-value *
		(FP/SAL)	(FP/FOR)	
ICS daily dose (µg)	Mean (SD)	1,256.8 (799.1)	1,346.6 (783.9)	0.005**
	Median (IQR)	1,068.5 (658,1808)	1,150.7 (658,2137)	
ICS daily dose (categorised) (µg)	0-450	23 (15.0)	21 (13.7)	0.016†
	451-750	23 (15.0)	26 (17.0)	
	751-1,000	28 (18.3)	18 (11.8)	
	1,001-1,500	29 (19.0)	SAMPLE	
	1,501-2,000	27 (17.6)	19 (12.4)	
SABA daily dose (µg)	Mean (SD)	2.3 (2.2)	2.3 (2)	0.957**
	Median (IQR)	1.9 (1,3)	1.9 (1,3)	
SABA daily dose (categorised) (µg)	0.01-1.00	31 (21.8)	30 (21.1)	0.549†
	1.01-2.00	40 (28.2)	40 (28.2)	
	2.01-3.50	40 (28.2)	37 (26.1)	
	3.51+	31 (21.8)	35 (24.6)	

Table 34: Mock table for ICS and SABA dose for ex-smokers

ICS and SABA dose categories for non-smokers

		Comparison between FP/SAL and FP/FOR (n = sample)		p-value *
		(FP/SAL)	(FP/FOR)	
ICS daily dose (µg)	Mean (SD)	1,256.8 (799.1)	1,346.6 (783.9)	0.005**
	Median (IQR)	1,068.5 (658,1808)	1,150.7 (658,2137)	
ICS daily dose (categorised) (µg)	0-450	23 (15.0)	21 (13.7)	0.016†
	451-750	23 (15.0)	26 (17.0)	
	751-1,000	28 (18.3)	18 (11.8)	
	1,001-1,500	29 (19.0)	SAMPLE	
	1,501-2,000	27 (17.6)	19 (12.4)	
SABA daily dose (µg)	Mean (SD)	2.3 (2.2)	2.3 (2)	0.957**
	Median (IQR)	1.9 (1,3)	1.9 (1,3)	
SABA daily dose (categorised) (µg)	0.01-1.00	31 (21.8)	30 (21.1)	0.549†
	1.01-2.00	40 (28.2)	40 (28.2)	
	2.01-3.50	40 (28.2)	37 (26.1)	
	3.51+	31 (21.8)	35 (24.6)	

Table 35: Mock table for ICS and SABA dose for non-smokers

ICS and SABA dose categories for patients classified as GINA stage III

		Comparison between FP/SAL and FP/FOR (n = sample)		p-value *
		(FP/SAL)	(FP/FOR)	
ICS daily dose (µg)	Mean (SD)	1,256.8 (799.1)	1,346.6 (783.9)	0.005**
	Median (IQR)	1,068.5 (658,1808)	1,150.7 (658,2137)	
ICS daily dose (categorised) (µg)	0-450	23 (15.0)	21 (13.7)	0.016†
	451-750	23 (15.0)	26 (17.0)	
	751-1,000	28 (18.3)	18 (11.8)	
	1,001-1,500	29 (19.0)	SAMPLE	
	1,501-2,000	27 (17.6)	19 (12.4)	
SABA daily dose (µg)	Mean (SD)	2.3 (2.2)	2.3 (2)	0.957**
	Median (IQR)	1.9 (1,3)	1.9 (1,3)	
SABA daily dose (categorised) (µg)	0.01-1.00	31 (21.8)	30 (21.1)	0.549†
	1.01-2.00	40 (28.2)	40 (28.2)	
	2.01-3.50	40 (28.2)	37 (26.1)	
	3.51+	31 (21.8)	35 (24.6)	

Table 36: Mock table for ICS and SABA dose for patients classified as GINA stage III

ICS and SABA dose categories for patients classified as GINA stage IV and V

		Comparison between FP/SAL and FP/FOR (n = sample)		p-value *
		(FP/SAL)	(FP/FOR)	
ICS daily dose (µg)	Mean (SD)	1,256.8 (799.1)	1,346.6 (783.9)	0.005**
	Median (IQR)	1,068.5 (658,1808)	1,150.7 (658,2137)	
ICS daily dose (categorised) (µg)	0-450	23 (15.0)	21 (13.7)	0.016†
	451-750	23 (15.0)	26 (17.0)	
	751-1,000	28 (18.3)	18 (11.8)	
	1,001-1,500	29 (19.0)	[illegible]	
	1,501-2,000	27 (17.6)	19 (12.4)	
SABA daily dose (µg)	Mean (SD)	2.3 (2.2)	2.3 (2)	0.957**
	Median (IQR)	1.9 (1,3)	1.9 (1,3)	
SABA daily dose (categorised) (µg)	0.01-1.00	31 (21.8)	30 (21.1)	0.549†
	1.01-2.00	40 (28.2)	40 (28.2)	
	2.01-3.50	40 (28.2)	37 (26.1)	
	3.51+	31 (21.8)	35 (24.6)	

Table 37: Mock table for ICS and SABA dose for patients classified as GINA stage IV and V

7. Adherence, MPR and controller to reliever ratio outcomes

		Comparison between FP/SAL and FP/FOR (n = sample)		p-value *
		(FP/SAL)	(FP/FOR)	
Adherence to ICS	Mean (SD) Median (IQR)	86.7 (39.1) 90.4 (58,107)	90.3 (35.4) 98.6 (66,115)	0.027**
Adherence to ICS (categorised)	0-70 71-100 101-120 121+	51 (33.3) 55 (35.9) 24 (15.7) 23 (15.0)	41 (26.8) 46 (30.1) 38 (24.8) 28 (18.3)	0.006†
Adherence to ICS (categorised)	0-70	51 (33.3)	41 (26.8)	0.078‡
	71+	102 (66.7)	[illegible]	
Medication possession ratio (MPR)	Mean (SD) Median (IQR)	51 (33.3) 102 (66.7)	41 (26.8) 112 (73.2)	0.023**
MPR (categorised)	0-80 81+	86.7 (39.1) 90.4 (58,107)	90.3 (35.4) 98.6 (66,115)	0.216‡
Controller to Reliever Ratio	Mean (SD) Median (IQR)	62 (40.5) 91 (59.5)	54 (35.3) 99 (64.7)	0.008**
Controller to Reliever Ratio (categorised)	<0.5 ≥0.5	0.62 (0.20) 0.56 (0.5,0.8)	0.65 (0.18) 0.61 (0.5,0.8)	0.038‡

Table 38: Mock table for ICS, MPR and controller to reliever ratios

Adherence, MPR and controller to reliever ratio outcomes for smokers

		Comparison between FP/SAL and FP/FOR (n = sample)		p-value *
		(FP/SAL)	(FP/FOR)	
Adherence to ICS	Mean (SD) Median (IQR)	86.7 (39.1) 90.4 (58,107)	90.3 (35.4) 98.6 (66,115)	0.027**
Adherence to ICS (categorised)	0-70 71-100 101-120 121+	51 (33.3) 55 (35.9) 24 (15.7) 23 (15.0)	41 (26.8) 46 (30.1) 38 (24.8) 28 (18.3)	0.006†
Adherence to ICS (categorised)	0-70	51 (33.3)	41 (26.8)	0.078‡
	71+	102 (66.7)	[illegible]	
Medication possession ratio (MPR)	Mean (SD) Median (IQR)	51 (33.3) 102 (66.7)	41 (26.8) 112 (73.2)	0.023**
MPR (categorised)	0-80 81+	86.7 (39.1) 90.4 (58,107)	90.3 (35.4) 98.6 (66,115)	0.216‡
Controller to Reliever Ratio	Mean (SD) Median (IQR)	62 (40.5) 91 (59.5)	54 (35.3) 99 (64.7)	0.008**
Controller to Reliever Ratio (categorised)	<0.5 ≥0.5	0.62 (0.20) 0.56 (0.5,0.8)	0.65 (0.18) 0.61 (0.5,0.8)	0.038‡

Table 39: Mock table for ICS, MPR and controller to reliever ratios for smokers

Adherence, MPR and controller to reliever ratio outcomes for ex-smokers

		Comparison between FP/SAL and FP/FOR (n = sample)		p-value *
		(FP/SAL)	(FP/FOR)	
Adherence to ICS	Mean (SD) Median (IQR)	86.7 (39.1) 90.4 (58,107)	90.3 (35.4) 98.6 (66,115)	0.027**
Adherence to ICS (categorised)	0-70 71-100 101-120 121+	51 (33.3) 55 (35.9) 24 (15.7) 23 (15.0)	41 (26.8) 46 (30.1) 38 (24.8) 28 (18.3)	0.006†
Adherence to ICS (categorised)	0-70	51 (33.3)	41 (26.8)	0.078‡
	71+	102 (66.7)	112 (73.2)	
Medication possession ratio (MPR)	Mean (SD) Median (IQR)	51 (33.3) 102 (66.7)	41 (26.8) 112 (73.2)	0.023**
MPR (categorised)	0-80 81+	86.7 (39.1) 90.4 (58,107)	90.3 (35.4) 98.6 (66,115)	0.216‡
Controller to Reliever Ratio	Mean (SD) Median (IQR)	62 (40.5) 91 (59.5)	54 (35.3) 99 (64.7)	0.008**
Controller to Reliever Ratio (categorised)	<0.5 ≥0.5	0.62 (0.20) 0.56 (0.5,0.8)	0.65 (0.18) 0.61 (0.5,0.8)	0.038‡

Table 40: Mock table for ICS, MPR and controller to reliever ratios for ex-smokers

Adherence, MPR and controller to reliever ratio outcomes for non-smokers

		Comparison between FP/SAL and FP/FOR (n = sample)		p-value *
		(FP/SAL)	(FP/FOR)	
Adherence to ICS	Mean (SD) Median (IQR)	86.7 (39.1) 90.4 (58,107)	90.3 (35.4) 98.6 (66,115)	0.027**
Adherence to ICS (categorised)	0-70 71-100 101-120 121+	51 (33.3) 55 (35.9) 24 (15.7) 23 (15.0)	41 (26.8) 46 (30.1) 38 (24.8) 28 (18.3)	0.006†
Adherence to ICS (categorised)	0-70	51 (33.3)	41 (26.8)	0.078‡
	71+	102 (66.7)	112 (73.2)	
Medication possession ratio (MPR)	Mean (SD) Median (IQR)	51 (33.3) 102 (66.7)	41 (26.8) 112 (73.2)	0.023**
MPR (categorised)	0-80 81+	86.7 (39.1) 90.4 (58,107)	90.3 (35.4) 98.6 (66,115)	0.216‡
Controller to Reliever Ratio	Mean (SD) Median (IQR)	62 (40.5) 91 (59.5)	54 (35.3) 99 (64.7)	0.008**
Controller to Reliever Ratio (categorised)	<0.5 ≥0.5	0.62 (0.20) 0.56 (0.5,0.8)	0.65 (0.18) 0.61 (0.5,0.8)	0.038‡

Table 41: Mock table for ICS, MPR and controller to reliever ratios for non-smokers

Adherence, MPR and controller to reliever ratio outcomes for patients classified with GINA stage III[3]

		Comparison between FP/SAL and FP/FOR (n = sample)		p-value *
		(FP/SAL)	(FP/FOR)	
Adherence to ICS	Mean (SD) Median (IQR)	86.7 (39.1) 90.4 (58,107)	90.3 (35.4) 98.6 (66,115)	0.027**
Adherence to ICS (categorised)	0-70 71-100 101-120 121+	51 (33.3) 55 (35.9) 24 (15.7) 23 (15.0)	41 (26.8) 46 (30.1) 38 (24.8) 28 (18.3)	0.006†
Adherence to ICS (categorised)	0-70	51 (33.3)	41 (26.8)	0.078‡
	71+	102 (66.7)	[illegible]	
Medication possession ratio (MPR)	Mean (SD) Median (IQR)	51 (33.3) 102 (66.7)	41 (26.8) 112 (73.2)	0.023**
MPR (categorised)	0-80 81+	86.7 (39.1) 90.4 (58,107)	90.3 (35.4) 98.6 (66,115)	0.216‡
Controller to Reliever Ratio	Mean (SD) Median (IQR)	62 (40.5) 91 (59.5)	54 (35.3) 99 (64.7)	0.008**
Controller to Reliever Ratio (categorised)	<0.5 ≥0.5	0.62 (0.20) 0.56 (0.5,0.8)	0.65 (0.18) 0.61 (0.5,0.8)	0.038‡

Table 42: Mock table for ICS, MPR and controller to reliever ratios for patients classified with GINA stage III[3]

Adherence, MPR and controller to reliever ratio outcomes[w] for patients classified with GINA stage IV and V[3]

		Comparison between FP/SAL and FP/FOR (n = sample)		p-value *
		(FP/SAL)	(FP/FOR)	
Adherence to ICS	Mean (SD) Median (IQR)	86.7 (39.1) 90.4 (58,107)	90.3 (35.4) 98.6 (66,115)	0.027**
Adherence to ICS (categorised)	0-70 71-100 101-120 121+	51 (33.3) 55 (35.9) 24 (15.7) 23 (15.0)	41 (26.8) 46 (30.1) 38 (24.8) 28 (18.3)	0.006†
Adherence to ICS (categorised)	0-70	51 (33.3)	41 (26.8)	0.078‡
	71+	102 (66.7)	[illegible]	
Medication possession ratio (MPR)	Mean (SD) Median (IQR)	51 (33.3) 102 (66.7)	41 (26.8) 112 (73.2)	0.023**
MPR (categorised)	0-80 81+	86.7 (39.1) 90.4 (58,107)	90.3 (35.4) 98.6 (66,115)	0.216‡
Controller to Reliever Ratio	Mean (SD) Median (IQR)	62 (40.5) 91 (59.5)	54 (35.3) 99 (64.7)	0.008**
Controller to Reliever Ratio (categorised)	<0.5 ≥0.5	0.62 (0.20) 0.56 (0.5,0.8)	0.65 (0.18) 0.61 (0.5,0.8)	0.038‡

Table 43: Mock table for ICS, MPR and controller to reliever ratios for patients classifed with GINA stage IV and V[3]

8. Treatment Stability

Treatment Stabilty	Treatment Group		Total
	FP/SAL	*FP/FOR*	
Successful n (%)	727 (63.4)	263 (68.8)	990 (64.8)
Unsuccessful n (%)	419 (36.6)	[illegible]	538 (35.2)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders (95% CI)	1.00	1.24 (0.95, 1.62)	

Table 44: Mock table for treatment stability

[w] See Section 14.1 for full definitions

Treatment stability for smokers

Treatment Stabilty	Treatment Group		Total
	FP/SAL	FP/FOR	
Successful n (%)	727 (63.4)	263 (68.8)	990 (64.8)
Unsuccessful n (%)	419 (36.6)	SAMPLE	538 (35.2)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders (95% CI)	1.00	1.24 (0.95, 1.62)	

Table 45: Mock table for treatment stability for smokers

Treatment stability for ex-smokers

Treatment Stabilty	Treatment Group		Total
	FP/SAL	FP/FOR	
Successful n (%)	727 (63.4)	263 (68.8)	990 (64.8)
Unsuccessful n (%)	419 (36.6)	SAMPLE	538 (35.2)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders (95% CI)	1.00	1.24 (0.95, 1.62)	

Table 46: Mock table for treatment stability for ex-smokers

Treatment stability for non-smokers

Treatment Stabilty	Treatment Group		Total
	FP/SAL	FP/FOR	
Successful n (%)	727 (63.4)	263 (68.8)	990 (64.8)
Unsuccessful n (%)	419 (36.6)	SAMPLE	538 (35.2)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders (95% CI)	1.00	1.24 (0.95, 1.62)	

Table 47: Mock table for treatment stability for non-smokers

Treatment stability for patients classified with GINA stage III[3]

Treatment Stabilty	Treatment Group		Total
	FP/SAL	FP/FOR	
Successful n (%)	727 (63.4)	263 (68.8)	990 (64.8)
Unsuccessful n (%)	419 (36.6)	SAMPLE	538 (35.2)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders (95% CI)	1.00	1.24 (0.95, 1.62)	

Table 48: Mock table for treatment stability for patients classified for GINA stage III[3]

Treatment stability for patients classified with GINA stage IV and V

Treatment Stabilty	Treatment Group		Total
	FP/SAL	FP/FOR	
Successful n (%)	727 (63.4)	263 (68.8)	990 (64.8)
Unsuccessful n (%)	419 (36.6)	SAMPLE	538 (35.2)
Total n (%)	1146 (100)	382 (100)	1528 (100)
Odds Ratio adjusted for baseline confounders (95% CI)	1.00	1.24 (0.95, 1.62)	

Table 49: Mock table for patients classified with GINA stage IV and V[3]

9. Hospitalisations for asthma and respiratory causes

In-patient Admissions for Asthma and LRTI causes	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	1142 (99.7)	380 (99.5)	1522 (99.6)
1+ n (%)	4 (0.3)	SAMPLE	6 (0.4)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 50: Mock table for asthma and respiratory hospitalisations

Hospitalisations for asthma and respiratory causes for smokers

In-patient Admissions for Asthma and LRTI causes	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	1142 (99.7)	380 (99.5)	1522 (99.6)
1+ n (%)	4 (0.3)	SAMPLE	6 (0.4)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 51: Mock table for asthma and respiratory hospitalisations for smokers

Hospitalisations for asthma and respiratory causes for ex-smokers

In-patient Admissions for Asthma and LRTI causes	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	1142 (99.7)	380 (99.5)	1522 (99.6)
1+ n (%)	4 (0.3)	SAMPLE	6 (0.4)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 52: Mock table for asthma and respiratory hospitalisations for ex-smokers

Hospitalisations for asthma and respiratory causes for non-smokers

In-patient Admissions for Asthma and LRTI causes	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	1142 (99.7)	380 (99.5)	1522 (99.6)
1+ n (%)	4 (0.3)	SAMPLE	6 (0.4)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 53: Mock table for asthma and respiratory hospitalisations for non-smokers

Hospitalisations for asthma and respiratory causes for patients classified with GINA stage III[3]

In-patient Admissions for Asthma and LRTI causes	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	1142 (99.7)	380 (99.5)	1522 (99.6)
1+ n (%)	4 (0.3)	SAMPLE	6 (0.4)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 53: Mock table for asthma and respiratory hospitalisations for patients classified with GINA stage III[3]

Hospitalisations for asthma and respiratory causes for patients classified with GINA stage IV and V[3]

In-patient Admissions for Asthma and LRTI causes	Treatment Group		Total
	FP/SAL	FP/FOR	
None n (%)	1142 (99.7)	380 (99.5)	1522 (99.6)
1+ n (%)	4 (0.3)	[illegible]	6 (0.4)
Total (n)	1146 (100)	382 (100)	1528 (100)

Table 54: Mock table for asthma and respiratory hospitalisations for patients classified with GINA stage IV and V[3]

10. Respiratory drug costs including/excluding FDC ICS/LABA drug costs

		Treatment Group		TOTAL (£)	p-value*
		FP/SAL(£)	FP/FOR(£)		
Asthma drug costs including ICS/LABA	N (% non-missing) Mean (SD) Median (IQR)	1146 (100) 344.03 (220.40) 297 (192, 432)	382 (100) [illegible] [illegible]	1528 (100) 348.54 ([illegible].60) 30[illegible] ([illegible]6, 440)	0.082
Asthma drug costs excluding ICS/LABA	N (% non-missing) Mean (SD) Median (IQR)	1146 (100) 41.16 (73.83) 18.05 (6, 39.19)	382 (100) 37.89 (74.94) 14.98 (5.63, 32.02)	1528 (100) 40.34 (74.1) 17.28 (6, 37.6)	0.417

Table 55: Mock table for drug costs
*conditional logistic regression

11. Cost of respiratory related resource utilisation (including LRTI coded resource utilisation)

		Treatment Group		TOTAL (£)	p-value *
		FP/SAL(£)	FP/FOR(£)		
Respiratory-related hospital admissions	N (% non-missing) Mean (SD) Median (IQR)	1146 (100) 417.86 (258.59) 369 (234, 517)	382 (100) 326.39 (184.35) [illegible]	1528 (100) 394.99 (245.34) [illegible]	<0.001
Respiratory-related GP consultations	N (% non-missing) Mean (SD) Median (IQR)	1146 (100) 48.12 (87.83) 17.45 (7.5, 41.34)	382 (100) 43.56 (98.22) 14.97 (5.96, 33.9)	1528 (100) 46.98 (90.53) 17.28 (7.08, 39.05)	0.353

Table 56: Mock table for hospital admission costs

12. Individual drug costs breakdown (fixed dose combination inhalers)

		Costs (£)			
		FP/SAL	FP/FOR	Total	P-value*
Fixed dose combination inhaler	N (% non-missing) Mean (SD) Median (IQR)	1146 (100) 368.20 (221.3[illegible]) 342.69 (210.00, 466.87)	382 (100) [illegible] 263.88 (196.80, 351.84)	1528 (100) 346.18 (205.47) 315.00 (210.00, 432.13)	<0.001

Table 57: Mock table for FDC drug costs

13. Other asthma related drug costs breakdown

		Costs (£)			
		FP/SAL	FP/FOR	Total	P-value*
Leukotriene receptor antagonists (LTRA)	N (% non-missing) Mean (SD) Median (IQR)	1146 (100) 20.09 (74.72) 0 (0, 0)	382 (100) 14.29 (62.6) 0 (0, 0)	1528 (100) 18.64 (71.91) 0 (0, 0)	0.157
Theophylline	N (% non-missing) Mean (SD) Median (IQR)	1146 (100) 0.55 (5.15) 0 (0, 0)	382 (100) SAMPLE 0 (0, 0)	1528 (100) 0.64 (5.83) 0 (0, 0)	0.354
Total Antibiotics	N (% non-missing) Mean (SD) Median (IQR)	1146 (100) 6.12 (21.94) 1.2 (0, 4.55)	382 (100) 6.29 (36.68) 0 (0, 3.84)	1528 (100) 6.16 (26.4) 1.16 (0, 4.5)	0.912
Total Oral Steroids - Prednisolone	N (% non-missing) Mean (SD) Median (IQR)	1146 (100) 2.33 (9.73) 0 (0, 0)	382 (100) 1.49 (10.68) 0 (0, 0)	1528 (100) 2.12 (9.98) 0 (0, 0)	0.153

Table 58: Mock table for respiratory drug costs

14. Short acting and long acting beta agonists cost breakdown

		Costs (£)			
		FP/SAL	FP/FOR	Total	P-value*
Short acting beta$_2$ agonist (SABA)	N (% non-missing) Mean (SD) Median (IQR)	1146 (100) 16.82 (22.44) 11 (5, 23)	382 (100) 16.4 (32.52) 9 (3, 20)	1528 (100) 16.71 (25.33) 9 (3, 21)	0.750
Long acting beta$_2$ agonist (LABA)	N (% non-missing) Mean (SD) Median (IQR)	1146 (100) 0.66 (9.84) 0 (0, 0)	SAMPLE 1.76 (22.32) 0 (0, 0)	1528 (100) 0.94 (14.04) 0 (0, 0)	0.227

Table 59: Mock table for beta agonist costs