Real-world effectiveness of extrafine versus standard particle ICS

A comparative effectiveness analysis of extrafine (EF) hydrofluoroalkane beclometasone (HFA-BDP) and Ciclesonide versus commonly prescribed standard particle inhaled corticosteroids for patients prescribed asthma therapy in The Netherlands.

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TABLE OF CONTENT

BACKGROUND

Current asthma guidelines are underpinned by evidence derived from randomised controlled trials (RCTs). Although RCT data are considered the gold standard, patients recruited to asthma RCTs are estimated to represent only a small percentage of the real-world asthma population.[i,ii,iii] The poor representation of the asthma population is due to a number of factors, such as tightly-controlled inclusion criteria for RCTs. There is, therefore, a need to carry out real-world observational studies to inform existing guidelines on the effectiveness of available treatments as used in every-day clinical practice in the heterogeneous asthma population.

Asthma management guidelines recommend long-term, daily anti-inflammatory controller therapy to attenuate the chronic airway inflammation of persistent asthma.[iv,v,vi] The choice of inhaled corticosteroid can be guided by practical considerations (e.g., cost factors) as RCTs have so far failed to identify consistent, significant differences in outcomes among the available inhaled corticosteroids[vii,viii] and data from observational studies are lacking.

RESEARCH HYPOTHESIS

Owing to similarity of efficacy of EF-HFA-BDP and fluticasone proprionate (FP) suggested by RCTs, and the even lung distribution afforded by the smaller HFA aerosol particles, we hypothesise that the EF-ICSs EF-HFA-BDP and Ciclesonide may be at least as effective (in terms of asthma control) as other commonly prescribed standard particle (SP) ICS therapies, such as SP-BDP and FP delivered via pressurised-metered dose inhalers (pMDI). This hypothesis was supported by retrospective database studies of EF-HFA-BDP versus FP using the UK's General Practice Research Database (GPRD)[ix,x] and the USA Ingenix Normative Healthcare Databse[xi]. The studies both found that EF-HFA-BDP patients achieved equal, or better, asthma outcomes than FP patients (matched on baseline disease severity and demography), but at significantly lower prescribed doses.

AIM

The aim of this study is to compare effectiveness (in terms of asthma control) of EF-ICS and SP-ICS therapies in patients from The Netherlands prescribed asthma therapy. In order to do so, we will compare the effectiveness of initiating ICS therapy as EF-HFA-BDP (Qvar®) pressurised metered dose inhaler (pMDI) or Ciclesonide vs. the most prescribed SP-ICS therapies in The Netherlands. The exact comparators were selected based on patient numbers receiving different ICS therapies within the supplied dataset and included FP and non-EF-HFA-BDP. The effects of increasing doses (≥50%) as EF or SP-ICS may also be

evaluated as a separate cohort (step-up cohort), but a decision on whether analysing this cohort or not will be made based on review of the results obtained for the initiation cohort.

DATA SOURCE

The analysis will be carried out using datasets available from the Pharmo Database Network (PDN), comprising:

- Pharmacy database, which provides pharmacy dispensing records linked with hospital discharge records for the 100% of the population within the PDN (almost 3 million patients accounting for approximately 20% of the Dutch population). Of each dispensed drug, the Anatomical Therapeutic Chemical (ATC) code, the dispensing date, the prescriber, the prescribed dosage regimen, the dispensed quantity, the costs and the estimated legend duration of use are available. The hospital data include detailed information about admission and discharge dates, primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, consultations with medical specialists and length of stay.
- The General Practice (GP) database which provides diagnosis, consultation and prescriptions information for a sub-population (about 5% of patients) in the PDN.
- The Clinical Laboratory Register (CLR) which can provide information regarding the requests for lung function tests issued by general practitioners and medical specialists for a sub-population (about 30% of patients) in the PDN.

The primary database to be used for the proposed analysis is the pharmacy database with linked hospitalisation data. Where it is not possible to link patients in the pharmacy database to their records in the GP database, the patients' drugs (pharmacy data) and secondary care records (hospital data) will be used to infer the patient's condition. Subgroup analyses of patients with linked GP and laboratory data can be performed as sensitivity analyses to validate the results depending on availability of these data.

STUDY DESIGN

This is a historic cohort effectiveness study consisting of a baseline and outcome period and an initiation date (ID).

The baseline period is a minimum of one year before ID for confounder definition and evaluation whether the analysis may benefit from matching. Matching criteria will be selected based on baseline differences in

demographic and clinical characteristics between treatment groups (see statistical methods for a full description of the matching process).

ID is the date at which asthma patients either:

(i) Initiated therapy as one of:

- EF-HFA-BDP pMDI
- Ciclesonide
- FP pMDI
- SP-BDP pMDI

OR (possibly)

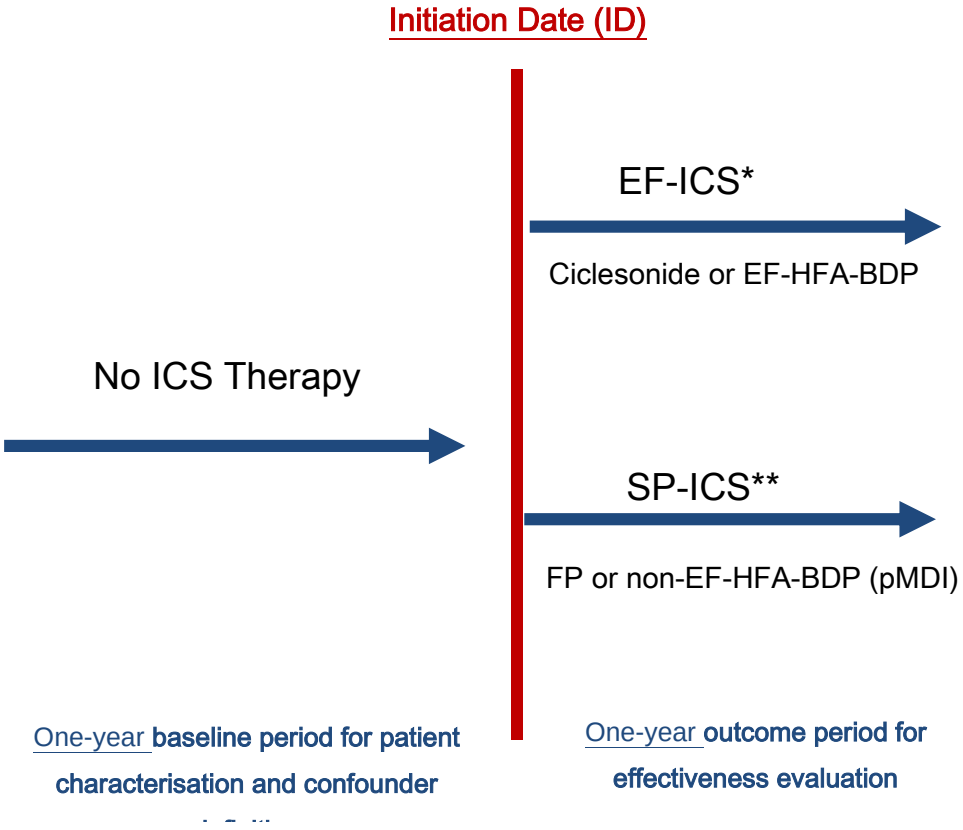
(ii) Increased their baseline ICS therapy as one of:

- EF-HFA-BDP pMDI
- Ciclesonide
- FP pMDI
- SP-BDP pMDI
- ICS/long-acting β2-agonist (LABA) therapy via pMDI
  – Fluticasone / salmeterol (FP/SAL)
  – Beclometasone / formoterol (BDP/FOR)

The outcome period is the one year period after ID and will be used to evaluate the consequences of initiating (or possibly increased) therapy as either EF-ICS or SP-ICS.

The study design is summarised in Figure 1.

Figure 1: Study Design



*Extra-fine ICS (median mass aerodynamic diameter [MAD] = 1 µm).
**Standard particle ICS (median MAD = 2-4 µm).

STUDY PERIOD

The study period will run from January 1998 to the end of December 2012. Patients included in the analysis will have at least 1-year of data prior to, and 1-year post ID (i.e., prior to/post the date of ICS initiation or increase). A 1-year period is estimated to be necessary to identify any measurable change in outcomes such as hospitalisations, and also allows for seasonal changes in respiratory disease and its related conditions.

STUDY POPULATION

The study population will be composed by patients prescribed asthma therapy in The Netherlands. Potential COPD patients (i.e. those over 60 years old) will be excluded.

Inclusion criteria

Patients must also meet the following inclusion criteria:

- Aged: 5-60 years:
    - Paediatric cohort (aged 5–11 years), and
    - Adult cohort (aged 12–60 years)

The "main" analysis will use the pharmacy (with linked hospital) database and will be reported for adult patients, with the option of a follow-up paediatric and adult analyses.

- Evidence of asthma:
    - Received ≥2 prescriptions for asthma in their records at different points in time at any time AND/OR
    - A diagnostic code for asthma – from hospital records or for patients with linked data from the general practice database
- Be receiving current ICS therapy
    - First prescription at ID plus
    - ≥2 ICS prescription during the outcome period (and for increasing cohort only: ≥1 ICS prescription during the baseline period)

- Have at least one full year of baseline data (prior to the ID) and at least one full year of outcome data (following the ID).

Exclusion criteria:

Patients will be excluded from the analysis if they:

- Had been diagnosed with any chronic respiratory disease at any time other than asthma (through hospital records or for patients with linked GP data)
- Have been prescribed ICS therapy during baseline including fixed dose combinations of ICS/LABA (applies to the initiation cohort only).
- Received maintenance oral steroid therapy[1] during baseline.
- Were prescribed multiple therapies at ID.

STUDY OUTCOMES

Co-Primary outcomes

(1) **Severe exacerbation rate in the year following ICS therapy initiation,** whereby severe exacerbations is defined based on the ATS/ERS Task Force definition[2] as:

- Asthma-related[3] hospital admissions **AND**
- Prescription for acute[4] courses of oral steroids[5]

(2) Modified definition for **Risk Domain Asthma Control (RDAC)**[6]**,** whereby asthma control is defined as:

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[1] Defined as:

- Patients less than 16 years old should not be on maintenance therapy
- For patients ≥16 years old, it is defined as <10mg Prednisolone or prescriptions for 1mg Prednisolone tablets per day and overall script coverage of more than 25% of days in a year.

[2] Please note that emergency department data are not included in the exacerbation definition due to these data not being available in the Pharmacy database, but emergency department events are likely captured by acute oral steroid use.

[3] Asthma-related defined as any hospital entry for asthma plus any lower respiratory reason (including lower respiratory tract infections).

[4] 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)
Whereby maintenance therapy is defined as above.

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

[6] Please note that both 'risk domain asthma control' and 'overall asthma control' definitions do not include the criterion of 'absence of evidence of GP consultations for LRTI' due to insufficient linked GP data in PHARMO database.

- Absence of asthma-related hospital admissions (as defined above) OR
- Absence of prescriptions for acute courses of oral steroids (as defined above)

(3) Modified definition for **Overall Asthma Control (OAC),** whereby asthma control was defined as

- Achieved RDAC (as defined above) **AND**
- Average daily dose of ≤200mcg salbutamol / ≤500mcg terbutaline

Secondary outcomes

(1) **Treatment stability** during outcome period, defined as:

- Achieved Risk Domain Asthma Control (as defined above)
- Addition of new therapy, including LTRA, THEO or LABA **OR**
- ICS dose increase by ≥50%
- Change ICS type and/or device (sensitivity definition only)

(2) **SABA usage**, evaluated in terms of average daily SABA dosage prescribed in the year following ICS therapy initiation, calculated as [(Count of inhalers * doses per inhalers / 365) * mcg strength] and categorised as appropriate to the data.

Exploratory outcomes

(1) Oral thrush prevalence

Number and percentage of patients who either received a diagnosis of oral thrush in their hospital records or received one or more topical oral anti-fungal prescriptions.

(2) Hospitalisations

Any hospital entry for asthma plus any lower respiratory reason (including lower respiratory tract infections).

COVARIATES

Prior research in respiratory disease has identified a range of potential confounders that may affect study outcomes. These include a range of demographic, disease severity, treatment and co-morbid factors. Exploratory analysis of these variables will be conducted to identify the key confounders, and outcome analyses will take these findings into account and select appropriate statistical methods (e.g. using logistic regression methods to account for confounding variables, using matching techniques to control for baseline differences) to minimise potential confounding.

Potential confounders examined at (or closest to) the ID:

- Age of patient
- Gender of patient
- Height and weight of patient (expressed as Body Mass Index (BMI)) if available
- Lung function, in terms of percent predicted peak flow readings[5] if available
- Smoking status if available
- First prescribed ICS dose
- Year of ID

Potential confounders examined regardless of when they occurred relative to the ID:

- Date of first asthma diagnosis if available
- Time of diagnosis relative to ID if available

Potential confounders examined in the year before and after the index date:

- Presence / absence of comorbid rhinitis (diagnosis ever and / or prescriptions for nasal sprays in the baseline / outcome year)
- Presence / absence of GERD (diagnosis ever and / or 2 or more prescriptions for proton pump inhibitor therapy in the baseline / outcome year
- Presence of cardiac disease (diagnosis ever and / or prescriptions for cardiac drugs in the baseline / outcome year)
- Where ICS have been prescribed, the average daily dose (in FP equivalents) based on prescriptions collected
- Average daily SABA dosage based on prescriptions collected
- Number of asthma or lower respiratory-related hospitalisations
- Other medications, number of prescriptions for the following in the year prior to IPD:
    - Paracetamol
    - Non-steroidal anti-inflammatory drugs (NSAIDs)
    - Beta-blocker prescriptions
    - Theophylline
    - Statins
    - Tricyclics

CODE LIST

The pharmacy database will use the ATC coding system – the Anatomical Therapeutic Chemical Classification System, a system of alphanumeric codes developed by the World Health Organization for the classification of drugs and other medical products. Subgroup R denotes the subgroup of codes relating to the respiratory system:

R= respiratory system; R01 = nasal preparations; R02 = throat preparations; R03 = drugs for obstructive airway disease; R05 = cough and cold preparations; R06 = antihistamies for systemic use; R07=other respiratory system products.

STATISTICAL ANALYSIS

Exploratory analysis

A full exploratory analysis of the above listed variables will be carried out for confounder definition and data familiarization. The decision on whether to carry out matched or unmatched analyses will be based on this exploratory analysis and will involve input from the Steering Committee.

Summary statistics

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

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

For categorical variables, the summary statistics will include:

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

Treatment groups will be compared using Mann Whitney U-test for variables measured on the interval/ratio scale and using a chi-square test for categorical variables.

Matching

Where baseline characteristics suggest significant ($p<0.05$) differences between Ciclesonide and comparator patients, matching may be performed to provide a more robust analysis. Patients will be matched on key demographic and asthma-related characteristics during the baseline year to ensure homogeneity. Criteria will be chosen based on baseline differences and clinical experience.

Patients will initially be matched on a 1:1 ratio, but other ratios will be considered based on maximising statistical power for the primary effectiveness outcome.

Analysis of co-primary effectiveness outcomes

Exacerbations rates in the outcome period will be compared between treatment groups using a negative binomial regression model. General estimating equations will be used to account for the correlation within matched pairs. The model will use empirical standard errors for more robust confidence intervals and adjust for potential baseline confounders. The adjusted rate ratio with 95% confidence interval will be reported.

The adjusted odds of achieving asthma control in the 1-year outcome (risk domain and overall definition), of achieving treatment stability and of being prescribed higher dose of SABA (higher dose category) will be compared between matched treatment groups using conditional logistic regression models. The dichotomous outcome of asthma control will be used as the dependent variable with treatment and potential confounding factors as explanatory variables. The adjusted odds ratio with 95% confidence interval will be reported.

Confounding factors

In order to minimise biases, confounders inferred from outcome prediction (through multivariable analysis, $p<0.05$), collinearity (through Spearman's correlation, $\rho>0.3$) and residual differences after matching (conditional logistic regression, $p<0.05$) will be adjusted for in the statistical model.

LIMITATIONS OF STUDY DESIGN, DATA SOURCES AND ANALYTICAL METHODS

As with all database studies, a number of limitations exist for which it is not possible to adjust and match (e.g., potential confounding factors with the problem of internal validity). Limitations could also arise from using the PHARMO database, including disease misclassification biases deriving from the almost exclusive use of "asthma prescriptions" to individuate asthmatic patients and the impossibility to fully adjust for confounding factors (e.g., potential confounding by severity for factors indiscernible from patient records or patient reported outcomes). In addition, study findings apply only to those healthier patients who survive at least one year after prescription date. Therefore there may be a potential survival bias.

The methods of adjustment described in the study design will be used to address all factors for which it is possible to account for.

ADVISORY GROUP

The advisory group will include a representative of the Small Airways Study Group (SASG):

- Richard Martin, Denver, Colorado, USA,
- Dirkje Postma, Groningen, The Netherlands
- Nicholas Roche, Paris, France
- Wim van Aalderen, The Netherlands

And Dutch experts:

- Richard Dekhuijzen, The Netherlands
- Thys van der Molen, The Netherlands

DATA DISSEMINATION

Once a final version of the protocol will be agreed and reviewed by the advisory group, this study will be registered with www.encepp.eu. Initial results will be presented in poster and/or oral 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 be made as soon as the analyses are completed and the results are verified.

COLLABORATORS

Research in Real Life research team

1. Professor David Price, General Practice Airways Group Professor of Primary Care Respiratory Medicine
2. Catherine Hutton, Project Director
3. Annie Burden, Senior Statistician
4. Vicky Thomas, Lead Statistician assigned to the project
5. Julie von Ziegenweidt, Data Manager
6. Emily Davis, Project Manager
7. Cristiana Miglio, Lead Researcher assigned to the project
8. Liz Hillyer, Communciations Director

Pharmo research team

1. Ron Herings, Scientific Director
2. Jetty Overbeek, Research Associate

Teva main contact

Gokul Gopalan, Senior Global Medical Director, Respiratory

ANNEX 1: DATA SPECIFICATION

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
Pharmacy	1 = Pharmacy data available, 0 = Not Available	n/a	Numeric	1				x	
Diagnostic	1 = Diagnostic and Consultation data available, 0 = Not Available for patient	n/a	Numeric	1		x			
Tests	1 = Function Lab data available, 0 = Not Available	n/a	Numeric	1					x
Hospital	1 = Hospital data available, 0 = Not Available	n/a	Numeric	1			x		
Unique_ID	Unique id for each patient row. Possible combination of Cohort, Patient ID and ID Date	n/a	Char	100		x		x	
Cohort	IPDI (Initiating ICS), IPDA (Increasing ICS dose), IPDA (add on LABA either as separate or as COMBO),IPDC (Change Device),IPDC (Change in ICS drug).	n/a	Char	4		x		x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
PatEID	Unique Patient ID - primary key linking same patient across all databases.	n/a	Char	50					
Category	Identifies which category of change occurred at ID for each patient: Init_ICS, Increase_ICS, Addon_LABA, Change_COMBO, Change_DEVICE, Change_ICSDrug	n/a	Char	5	Inhaled Corticosteroids (ICS), Long-Acting Bronchodilator (LABA), COMBO (Combination ICS & LABA Inhaler)	x		x	
Category_Code	1 = Initiating ICS, 2 = Increase ICS, 3 = Add on LABA, 4 = Change to COMBO, 5 = Change ICS Device, 6 = Change ICS drug substance.	n/a	Numeric	1					
ID_Date	Index prescription date	n/a	Date	10	yyyy-mm-dd	x		x	
Year_of_ID	Year of the ID_Date	n/a	Numeric	4					
Evidence_of_Asthma	Indicate if patient has either a Asthma diagnosis OR has been on active asthma therapy	n/a	Numeric	1	Refer to Asthma_Diagnosis And Active_Active_Therapy variables	x	x	x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
	1 = Yes, 0 = No.								
Active_Asthma_Therapy	Indicate if patient has had 2 or more Asthma scripts during baseline period. 1 = Yes, 0 = No.	n/a	Numeric	1	≥2 prescriptions for asthma at different points in time during the prior year. (SABA (ATC -R03AC),ICS (ATC -R03BA), LABA (ATC -R03AC), COMBO,(ATC -R03AK), LTRA (ATC -R03DC), THEO(ATC -R03DA))	x		x	
Current_Asthma_Therapy	Indicate if patient has at least 1 more ICS script in outcome period, and, if applicable, at least 1 ICS script in baseline period 1 = Yes, 0 = No	1 Year Prior ID and 1Year After ID	Numeric	1	Requires ≥2 prescription for "relevant therapy" during the outcome year (i.e. ≥1 prescription in addition to the prescription at index date.)	x		x	
Pharmo_Model_Ind	Indicate if patient matches the definition of an asthma based on their algorithm model.	1 Year Prior ID	Numeric	1	See reference for details	x			
Age	Age at ID Date	ID	Numeric	3	Ensure age of patient is relevant to study.	x		x	
Gender	0 = FEMALE, 1 = MALE	n/a	Numeric	1		x	x		
Reg_Hospital	Number of days patient has been registered on Hospital Database prior to ID.	Prior ID	Numeric	4	Days registered on database normally to be a **MINIMUM** of 365. or less than 365 for paediatrics aged < 1 year.		x		

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
Reg_Diagnostic	Number of days patient has been registered on Diagnostic database prior to ID.	Prior ID	Numeric	4	Days registered on database normally to be a **MINIMUM** of 365. or less than 365 for paediatrics aged < 1 year.	x			
Reg_Pharmacy	Number of days patient has been registered on Pharmacy database prior to ID.	Prior ID	Numeric	4	Days registered on database normally to be a **MINIMUM** of 365. or less than 365 for paediatrics aged < 1 year.			x	
Reg_Tests	Number of days patient has been registered on Test database prior to ID.	Prior ID	Numeric	4	Days registered on database normally to be a **MINIMUM** of 365. or less than 365 for paediatrics aged < 1 year.				x
DeReg_Hospital	Number of days patient has been registered on Hospital Database after ID. If still registered, use date of data extract as data end point.	After ID	Numeric	4	Days registered on database needs to be a **MINIMUM** of 365		x		
DeReg_Diagnostic	Number of days patient has been registered on Diagnostic database after ID. If still registered, use date of data extract as data end point.	After ID	Numeric	4	Days registered on database needs to be a **MINIMUM** of 365	x			
DeReg_Pharmacy	Number of days patient has been registered on Pharmacy database	After ID	Numeric	4	Days registered on database needs to be a **MINIMUM** of 365			x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
	after ID. If still registered, use date of data extract as data end point.								
DeReg_Tests	Number of days patient has been registered on Test database after ID. If still registered, use date of data extract as data end point..	After ID	Numeric	4	Days registered on database needs to be a **MINIMUM** of 365				x
Height	Height (m) - closest to ID	Closest to ID	Numeric	11,1	Adults - over 16 - Height: > 1.4 metres and < 2.2. Children over 5 and under 16 – Height: > 0.5 metres and < 2.2 Children under 5: Accept current values	x			
Height_Days	Number of Days between closest date of recorded height to the ID_Date.	Closest to ID	Numeric	10	+/-	x			
Weight	Weight (kg) - closest to ID	Closest to ID	Numeric	11,1	Adults - over 16 - Weight: > 40kg and < 200kg Children under 5: Accept current values Children over 5 and under 16 - Weight: > 10kg and < 200kg	x			
Weight_Days	Number of Days between closest date of recorded weight to the ID_Date.	Closest to ID	Numeric	10	+/-	x			

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
BMI	Calculated BMI for patient - kg / m2	Closest to ID	Numeric	3.1		x			
Smoking_Status	2 - Smoker 3 - Ex-Smoker 4 - Passive Smoker -1 - Unknown	Closest prior to ID.	Numeric	1	2 - Smoker ICD10 (Z72.0,F17.1),ICD9 3 - Ex-Smoker ICD10 (Z71.6) 4 - Passive Smoker ICD10 (Z758.7)	x	x	x	
Asthma_Diagnosis	Indicate if patient had ever had an Asthma Diagnosis: 0 = No, 1 = Yes	At any time	Numeric	1	ICD10 Codes (J45,J46), ICD9 Codes (493)	x	x		
Asthma_First_Diag	Number of days between asthma first diagnosed and ID date.	At any time	Numeric	10		x	x		
Asthma_Year_First_Diag	Year when asthma was first diagnosed	At any time	Numeric	4		x	x		
Asthma_Last_Diag	Number of days between asthma last diagnosed in dataset and date of ID.	At any time	Numeric	10		x	x		
Asthma_First_Rx	Number of days between date of first asthma script and date of ID.	At any time	Numeric	10		x		x	
Asthma_Diag_Earliest	Identify year which was first; diagnosis or asthma script	At any time	Numeric	4		x	x	x	
COPD Diagnosis	Indicate if patient has ever had a COPD code	At any time	Numeric	1	ICD10 Codes (J44) ICD9 Codes (49120, 49121, 49122)	x	x		

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
	recorded : 0 = No, 1 = Yes								
COPD_First_Diag	Number of days between date COPD first diagnosed and date of ID.	At any time	Numeric	10		x	x		
Rhinitis Diagnosis	Rhinitis Code: 0 = No, 1 = Yes	At any time	Numeric	1	ICD10 Codes (J31.0, J30) ICD9 Codes (4720, 477)	x	x		
Rhinitis_First_Diag	Number of days between date Rhinitis first diagnosed and date of ID.	At any time	Numeric	10		x	x		
Rhinitis_Dx_Nasal_Spray	Indicate if patient has ever had a Rhinitis Diagnosis and/or Nasal Spray prescribed in baseline or outcome period : 0 = No, 1 = Yes	Baseline and outcome.	Numeric	1	ATC Codes (R01AD,R01AX, R01B)	x		x	
Eczema_Diagnosis	Eczema code recorded: 0 = No, 1 = Yes	At any time	Numeric	1	ICD10 Codes (L20 - L30), ICD9 Codes (6908, 6910, 6918, 6920, 6921, 6922, 6923, 6924, 6925, 6926, 6929, 6930, 6931, 6938, 6939, 6965, 6980, 6981, 6982, 6983, 6988, 6989, 69010, 69011, 69012, 69018, 69281, 69283, 69284, 69289)	x	x		
Eczema_Dx_Drugs	Indicate if patient has ever had a Eczema Diagnosis and/or Topical Steroids	Baseline and outcome.	Numeric	1	ATC Codes - (D07)	x	x	x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
	prescribed in baseline or outcome period: 0 = No, 1 = Yes								
Other_Chronic_Dis	Indicate if patient has ever had any other Chronic pulmonary diseases diagnosed : 0 = No, 1 = Yes	At any time	Numeric	1	ICD10 Codes (J40-J43,J47,J60-J70) ICD9 Codes (500, 5001, 501, 5060, 5062, 5063, 5064, 5069, 5088, 5089, 515)	x	x		
GERD_Diagnosis	Indicate if patient has ever had a GERD read code : 0 = No, 1 = Yes	At any time	Numeric	1	ICD10 Codes (K21) ICD9 Codes (53081)	x	x		
GERD_Dx_Drugs	Indicate if patient has ever received drugs for GERD in baseline or outcome period and/or GERD diagnosis : 0 = No, 1 = Yes	Baseline and outcome.	Numeric	1	ATC Codes (A02BC)	x	x	x	
Cardiac_Diagnosis	Indicate if patient has ever had a Cardiac Disease code : 0 = No, 1 = Yes	At any time	Numeric	1	ICD10 Codes (I26-I28) ICD9 Codes (415 - 418)	x	x		
Cardiac_Dx_Drugs	Indicate if patient has ever received any drugs for Cardiac Disease in baseline or outcome period or/and Cardiac Disease Diagnosis :	Baseline and outcome	Numeric	1	ATC Codes - (C01, C02,C03,C07,C08,C09)	x	x	x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
	0 = No, 1 = Yes								
Beta_Blockers	0 = N – none received over period, 1 = Y – received over period	1 Year Prior & incl ID	Numeric	1	ATC Codes (C07)	x		x	
NSAIDS	0 = N – none received over period, 1 = Y – received over period	1 Year Prior & incl ID	Numeric	1	ATC Codes (M01AB)	x		x	
Paracetamol	0 = N – none received over period, 1 = Y – received over period	1 Year Prior & incl ID	Numeric	1	ATC Codes (N02BE01)	x		x	
Statins	0 = N – none received over period, 1 = Y – received over period	1 Year Prior & incl ID	Numeric	1	ATC Codes (C10AA)	x		x	
Tricyclics	0 = N – none received over period, 1 = Y – received over period	1 Year Prior & incl ID	Numeric	1	ATC Codes - (N06AA)	x		x	
BASELINE SPECIFIC VARIABLES - PRE ID									
ba_Asthma_Scripts	Count of scripts for asthma ONLY – grouped by patient and date	1 Year Prior ID	Numeric	11	ATC Codes (R03A, R03BB, R03DA, R03BA, R03BC, R03DC)	x		x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
ba_Allergy_Scripts	Count of any scripts for ALLERGIES only - grouped by patient and date	1 Year Prior & incl ID	Numeric	11	ATC Codes (R01AC, R01AD,R06, D04AA,S01G)	x		x	
ba_Asthma_InP	Count of in-patient hospital admissions for Asthma plus lower respiratory admissions (incl LRTI)	1 Year Prior & incl ID	Numeric	11		x	x		
ba_Asthma_InP_Vague	Count of in-patient hospital admissions for any Vague entry.	1 Year Prior & incl ID	Numeric	11	Vague defined as any generic hospital admission with an Asthma or Lower Respiratory diagnosis within +/- 7 days of entry. (incl LRTI).	x	x		
ba_Acute_OS	Count of total acute oral steroid scripts prescribed to patients to treat exacerbations	1 Year Prior & incl ID	Numeric	11	ATC Codes (A07EA)	x		x	
ba_Maint_OS	Count of maintenance steroid courses	1 Year Prior & incl ID	Numeric	11	ATC Codes (A07EA)	x		x	
ba_Maint_OS_Ind	Indicate if patient had maintenance oral steroids in baseline period: 1 = Yes, 0 = No	1 Year Prior & incl ID	Numeric	1		x		x	
ba_Total_OS	Total number of all oral steroid courses prescribed – acute and maintenance	1 Year Prior & incl ID	Numeric	11	ATC Codes (H02AB06, H02AB07)	x		x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
ba_Cand_Def	Count of definite oral candidiasis diagnosed	1 Year Prior ID	Numeric	11	ICD10 Codes (B37.0) ICD9 Codes (1120)	x	x		
ba_Antifungal_Def	Count of definite antifungal scripts that are only prescribed for oral thrush	1 Year Prior ID	Numeric	11	ATC Codes: (Nystatin A07AA02 O, Amphotericin A01AB04 O, Miconazole A01AB09 O, Miconazole A07AC01 O, Clotrimazole A01AB18, Minocycline A01AB23)	x		x	
ba_Cand_Anti_Def	Count of combined dates for definite oral thrush and definite Antifungals	1 Year Prior ID	Numeric	11		x	x	x	
ba_PF_BE	Typecode – 007R	Last recorded best ever reading prior to ID	Numeric	11,1	**For Paediatrics (aged 4-19):**	x			x
ba_PF_BE_ Days	Number of days between Date of best ever reading and date of ID.	Last recorded best ever reading prior to ID	Numeric	10	The basic equations used are:	x			x

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database	
ba_PF_BE_Hgt	Last Height recorded prior to date of best ever	Last recorded best ever reading prior to ID	Numeric	11,1	PEFR in litres per second for boys 4-19 years < 162.6 cm (Rosenthal) = (0.073 * (height in cm)) - 5.98	x			x	
ba_PF_BE_Hgt_Days	Number of days between Date of best ever height recorded AND date of ID.	Last recorded best ever reading prior to ID	Numeric	10	PEFR in litres per second for boys 4-19 years >= 162.6 cm (Rosenthal) = (0.125 * (height in cm)) - 13.14	x			x	
ba_PF_Current	Typecode – 007T	Last recorded current reading prior to ID	Numeric	11,1	PEFR in litres per second for girls 4-19 years < 152.6 cm (Rosenthal) = (0.079 * (height in cm)) - 6.79	x			x	
ba_PF_Curr_ Days	Number of days between Date of current result and date of ID.	Last recorded current reading prior to ID	Numeric	10	PEFR in litres per second for girls 4-19 years >= 152.6 cm (Rosenthal) = (0.064 * (height in cm)) - 3.94	x			x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
ba_PF_Curr_Hgt	Last Height recorded prior to date of current reading	Last recorded current reading prior to ID	Numeric	11,1	However, subjects must be > 0.86m tall (girls) or > 0.82m tall (boys) for these equations to be non-negative.	x			x
ba_PF_Curr_Hgt_ Days	Number of days between Date of current height recorded and date of ID.	Last recorded current reading prior to ID	Numeric	10	The following equation has been used for paediatrics (male & female) <= 1.1m tall:	x			x
ba_PF_Pred	Typecode – 007S	Last recorded pred. reading prior to ID	Numeric	11,1	PEFR in litres per second (Robinson from Cotes page 465) = (4.93 * (height in metres)) - 2.9	x			x
ba_PF_Pred_ Days	Number of days between Date of predicted result and date of ID.	Last recorded pred. reading prior ID	Numeric	10	Subjects must still be > 0.6m tall for a non-negative predicted PEFR.	x			x
ba_PF_Pred_Hgt	Last height taken prior to predicted recording	Last recorded pred. reading prior ID	Numeric	11,1		x			x
ba_PF_Pred_Hgt_ Days	Number of days between Date of height and ID.	Last recorded pred.	Numeric	10		x			x

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
		reading prior ID							
ba_Drug_Treatment	Description to identify asthma therapy	1 Year Prior ID	Char	100		x		x	
ba_Drug_Treatment_Code	Code to identify asthma therapy in baseline period	1 Year Prior ID	Numeric	2	1 = SABA 2 = SAAC 3 = SAAC + SABA 4 = LABA +/- SAAC +/- SABA 5 = LAMA +/- SAAC +/- SABA 6 = LABA + LAMA +/- SAAC +/- SABA 7 = ICS +/- SAAC +/- SABA 8 = ICS + LABA +/- SAAC +/- SABA 9 = ICS + LAMA +/- SAAC +/- SABA 10 = ICS + LABA + LAMA +/- SAAC +/- SABA 11 = LTRA +/- SAAC +/- SABA 12 = LABA + LTRA +/- SAAC +/- SABA 13 = LAMA + LTRA +/- SAAC +/- SABA 14 = ICS + LTRA +/- SAAC +/- SABA 15 = ICS + LAMA + LTRA +/- SAAC +/- SABA 16 = ICS + LABA + LAMA + LTRA +/- SAAC +/- SABA 17 = ICS + LABA + LTRA +/- SAAC +/- SABA	x		x	
ba_SABA_Scripts	No of SABA scripts	1 Year Prior ID	Numeric	11		x		x	
ba_SABA_Inhalers	No of SABA inhalers	1 Year Prior ID	Numeric	11		x		x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
ba_SABA_Daily_Dose	No of SABA doses per day	1 Year Prior ID	Numeric	11,1	(((Count of inhalers * doses in pack) / 365) * mcg strength) / average prescribing dosage for saba (ie 200mcg Salbutamol / 500mcg Terbutaline / 180mcg Albuterol) to get SABA Daily Dose. Ensure that the saba daily dosage * average prescribing dosage (ie 200mcg Salbutamol) equals SABA Daily Dosage	x		x	
ba_SABA_Daily_Dosage	Based on average number of puffs per day over the year x mcg	1 Year Prior ID	Numeric	17,2	((Count of inhalers * doses in pack) / 365) * mcg strength	x		x	
ba_ICS_Scripts	No of scripts issued in last 12 months	1 Year Prior ID	Numeric	11	Check that ICS scripts is relative to daily dose	x		x	
ba_ICS_Inhalers	No of inhalers issued in last 12 months	1 Year Prior ID	Numeric	11	Check that ICS inhalers is relative to ICS scripts.	x		x	
ba_ICS_Daily_Dose	No of ICS doses per day	1 Year Prior ID	Numeric	11,1	((Count of inhalers * doses in pack) / 365)	x		x	
ba_ICS_Daily_Dosage	Average mcg daily dose per day – Beclometasone equivalent	1 Year Prior ID	Numeric	17,2	((Count of inhalers * doses in pack) / 365) * mcg strength	x		x	
ba_ICS_Total_Dosage	Total dosage in micrograms prescribed in baseline period – bdp	1 Year Prior ID	Numeric	11		x		x	
ba_ICS_Duration	Total Pack Days	1 Year Prior ID	Numeric	17	Sum (Number doses in pack / Prescribing instructions)	x		x	
ba_ICS_Actual_Period	Actual prescription days.	1 Year Prior ID	Numeric	17	(date of last script - date of first script) + Number pack days of last script	x		x	
ba_ICS_Drug_1	Product Name of LAST ICS drug issued prior to	1 Year Prior ID	Char	200	This is the last ICS prescribed to patient. prior to ID.	x		x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
	ID date – 1st drug if multiple drugs issued on same day. - 2 = N/A				Not applicable for IPDI cohort.				
ba_ICS_Last_Dose_1	Last prescribed ICS dosage prior to ID for ICS Drug 1. - 2 = N/A	1 Year Prior ID	Numeric	11		x		x	
ba_ICS_Device_1	ICS Drug 1 device – 0 = MDI, 1 = DPI. - 2 = N/A	1 Year Prior ID	Numeric	1		x		x	
ba_ICS_Subst_1	ICS Drug 1 Substance type – 0 = Beclometasone, 1 = Fluticasone, 2 = Mometasone, 3 = Budesonide, 4 = Ciclesonide - 2 = N/A	1 Year Prior ID	Numeric	1		x		x	
ba_ICS_Drug_2	Product Name of last ICS drug issued prior to ID date – 2nd drug if multiple drugs issued on same day. Else indicate a -2 code for N/A.	1 Year Prior ID	Char	200	Drug 2 only applicable is patient was prescribed MULTIPLE ICS scripts on the same day immediately prior to ID. Not applicable for IPDI cohort.	x		x	
_ICS_Device_2	ICS Drug 2 device – 0 = MDI, 1 = DPI. -2 = N/A.	1 Year Prior ID	Numeric	1		x		x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
ba_ICS_Subst_2	ICS Drug 2 Substance type – 0 = Beclometasone, 1 = Fluticasone, 2 = Mometasone, 3 = Budesonide, 4 = Ciclesonide -2 = N/A	1 Year Prior ID	Numeric	1		x		x	
ba_LABA	Indicate if patient received LABA in baseline period : 0 = No, 1 = Yes	1 Year Prior ID	Numeric	1	ATC -R03AC	x		x	
ba_LABA_Rx	No of LABA scripts patient was prescribed	1 Year Prior ID	Numeric	11	ATC -R03AC	x		x	
ba_LTRA	Indicate if patient received LTRA in baseline period. 0 = No, 1 = Yes	1 Year Prior ID	Numeric	1	ATC -R03DC	x		x	
ba_LTRA_Rx	No of LTRA scripts issued to patient	1 Year Prior ID	Numeric	1	ATC -R03DC	x		x	
ba_THEO_Rx	No of Theophylline scripts issued to patient	1 Year Prior ID	Numeric	11	ATC -R03DA	x		x	
ba_Spacer_Device	Indicate if patients were issued with a spacer device: 1 = Yes, 0 = No. -2 = N/A	1 Year Prior ID	Numeric	1	Not applicable to IPDI cohort.	x		x	
OUTCOME VARIABLE - POST ID									

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
ID_ICS_Drug_Name	ICS/COMBO drug product name issued AT ID date	At ID	Char	200		x		x	
ID_ICS_Dose	Actual prescribing dosage at ID: Prescrib. instructions * strength in bdp-eqv.	At ID	Numeric	11	Please Note: If patient on Self-management Program, assume 2 puffs twice daily for MDI device or 1puff twice daily for DPI device.	x		x	
ID_ICS_Device	ICS/COMBO Drug device AT ID - 0 = MDI, 1 = DPI	At ID	Numeric	1		x		x	
ID_HFA_Type	Indicate if drug is a HFA-BDP and what brand: 0 = No, 1 = QVAR, 2 = CLENIL	At ID	Numeric	1					
ID_ICS_Drug_Substance	ICS drug substance prescribed at ID – 0 = Beclometasone, 1 = Fluticasone, 2 = Budesonide	At ID	Numeric	1		x		x	
ID_FDC_Inhaler	If step up in ICS drug is to a Fixed Dose combo Inhaler, indicate which type: - 0 - No, 1 = FP/SAL, 2 = BUD/FOR, 3 = BDP/FOR	At ID	Numeric	1	Applicable to IPDA - Change COMBO category.	x		X	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
ID_LABA_Drug	LABA Drug Product Name AT ID date.	At ID	Numeric	1	Applicable to IPDA - Addon LABA category.	x		x	
ID_LABA_Substance	LABA drug substance - 1 = Salmeterol, 2 = Formoterol.	At ID	Numeric	1	Applicable to IPDA - Addon LABA category.	X		x	
out_LABA/ICS_First_Days	Number of days between date of ID (LABA rx) and FIRST ICS script.	3 Months After ID (incl ID)	Numeric	11	Applicable to IPDA - Addon LABA category. If ICS was not prescribed on same day as LABA, then take first ICS rx in 3 months after ID. If not found, assume same drug and instructions for last ICS prior ID.				
out_ICS_First_Dose	First ICS script dose after ID: prescrib. instructions * strength in bdp-eqv.	1 Year After ID	Numeric	11		x		x	
out_Asthma_Scripts	Count of scripts for asthma only – grouped by patient and date	1 Year After & incl ID	Numeric	11	ATC Codes (R03A, R03BB, R03DA, R03AK, R03BA, R03BC, R03DC)	x		x	
out_Allergy_Scripts	Count of scripts for ALLERGIES only - grouped by patient and date	1 Year After ID	Numeric	11	ATC Codes (R01AC, R01AD,R06, D04AA,S01G)	x		x	
out_Asthma_InP	Count of in-patient hospital admissions for Asthma plus lower respiratory admissions (incl LRTI)	1 Year After ID	Numeric	11		x		x	
out_Asthma_InP_Vag	Count of in-patient hospital admissions for Asthma plus lower	1 Year After ID	Numeric	11	Ensure that this contains the definite Asthma admissions as well.	x		x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
	respiratory admissions (incl LRTI) as well as any vague admissions								
out_Asthma_OPD	Count of out-patient hospital attendances for Asthma plus lower resp admissions (incl LRTI)	1 Year After ID	Numeric	11		x		x	
out_Acute_OS	Count of all acute oral steroid scripts issued to patient	1 Year After ID	Numeric	11	ATC Codes (A07EA)	x		x	
out_Maint_OS	Count of definite maintenance oral steroid courses	1 Year After ID	Numeric	11	ATC Codes (A07EA)	x		x	
out_Total_OS	Total number of all oral steroid courses prescribed	1 Year After ID	Numeric	11	ATC Codes (A07EA)	x		x	
out_LRTI_Consults	Count of all consultations for a Lower Respiratory Tract Infection treated with Antibiotics	1 Year After ID	Numeric	11	ICD10 Codes (J20-J22) ICD9 Codes (466) ATC Codes (A07AA)	x		x	
out_Cand_Def	Count of definite oral candidiasis diagnosed	1 Year After ID (inc ID)	Numeric	11	ICD10 Codes (B37.0) ICD9 Codes (1120)	x	x		
out_Antifungal_Def	Count of definite antifungal scripts that are only prescribed for oral thrush	1 Year After ID (inc ID)	Numeric	11	ATC Codes: (Nystatin A07AA02 O, Amphotericin A01AB04 O, Miconazole A01AB09 O,	x		x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
					Miconazole A07AC01 O, Clotrimazole A01AB18, Minocycline A01AB23)				
out_Cand_Anti_Def	Count of combined dates for definite oral thrush and definite Antifungals	1 Year After ID (inc ID)	Numeric	11		x		x	
out_SABA_Scripts	No of SABA scripts	1 Year After ID (inc ID)	Numeric	11	Check that the saba scripts is in relation to saba daily dose.	x		x	
out_SABA_Inhalers	No of SABA inhalers	1 Year After ID (inc ID)	Numeric	11	Check that the saba inhalers is relative to saba scripts.	x		x	
out_SABA_Daily_Dose	Average no of SABA doses per day	1 Year After ID (inc ID)	Numeric	11,1	(((Count of inhalers * doses in pack) / 365) * mcg strength) / average prescribing dosage for saba (ie 200 mcg Salbutamol / 500mcg Terbutaline / 180mcg Albuterol) to get SABA Daily Dose. Ensure that the saba daily dosage * average prescribing dosage (ie 200mcg Salbutamol) equals SABA Daily Dosage	x		x	
out_SABA_Daily_Dosage	Based on average number of SABA puffs per day over the year x strength in mcg	1 Year After ID (inc ID)	Numeric	11,2	((Count of inhalers * doses in pack) / 365) * mcg strength	x		x	
out_ICS_Daily_Dose	Average no of ICS doses per day	1 Year After ID (inc ID)	Numeric	11,1	((Count of inhalers * doses in pack) / 365)	x		x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
out_ICS_Daily_Dosage	Average ICS daily dosage (mcg BDP eqv) - average daily puff of ICS	1 Year After ID(inc ID)	Numeric	11,2	((Count of inhalers * doses in pack) / 365) * mcg strength	x			
out_ICS_Scripts	No of scripts prescribed in the next 12 months	1 Year After ID (inc ID)	Numeric	11	Check that ICS scripts is relative to daily dose	x		x	
out_ICS_Inhalers	No of inhalers issued in the next 12 months	1 Year After ID (inc ID)	Numeric	11	Check that ICS inhalers is relative to ICS scripts.	x		x	
out_ICS_Total_Dosage	Total dosage in micrograms prescribed in outcome period – bdp	1 Year After ID (inc ID)	Numeric	11		x		x	
out_ICS_Duration	Total Pack Days	1 Year After ID (inc ID)	Numeric	17	Sum (Number doses in pack / Prescribing instructions)	x		x	
out_ICS_Actual_Period *	Actual prescription days.	1 Year After ID (inc ID)	Numeric	17	(date of last script - date of first script) + Number pack days of last script	x		x	
out_Spacer_Device	Indicate if patients were issued with a spacer device: 1 = Yes, 0 = No	1 Year After ID (inc ID)	Numeric	1		x		x	
out_ICS_Last_Dose	Indicate last ICS dose prescribed to patient during outcome period. Based on prescribed	1 Year After ID	Numeric	11		x		x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
	dose * mcg strength in bdp-eqv.								
out_ICS_DaysDiff	No of days between ID and last ICS issued to patient	1 Year After ID	Numeric	11		x		x	
out_LABA	Indicate if patient receives any LABA in outcome period	1 Year After ID	Numeric	1	ATC -R03AC	x		x	
out_LABA_Rx	Number of LABA scripts issued to patient	1 Year After ID	Numeric	11	ATC -R03AC	x		x	
out_LTRA	Indicate if patient received any LTRA in outcome period	1 Year After ID	Numeric	1	ATC -R03DC	x		x	
out_LTRA_Rx	Number of LTRA scripts issued to patient	1 Year After ID	Numeric	11	ATC -R03DC	x		x	
out_THEO_Rx	Number of Theophylline scripts issued to patient	1 Year After ID	Numeric	11	ATC -R03DA	x		x	
Change_In_Therapy	Indicate if patient had a change in therapy in the outcome period ie increase in ICS (>=50%) or change in ICS drug or inhaler device or the add on of	1 Year After ID	Numeric	1		x		x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
	Theophylline or LTRA: 1 = Yes, 0 = No								
Increase_In_ICS_1st	Indicate if their first change in therapy was as an increase in ICS. Yes, 0 = No	1 Year After ID	Numeric	1		x		x	
Increase_In_ICS_Days	Number of days between date of ID and date of FIRST change as an Increase in ICS.	1 Year After ID	Numeric	10		x		x	
Change_in_Drug_1st	Indicate if their first change in therapy was a change in their ICS drug type: 1 = Yes, 0 = No	1 Year After ID	Numeric	1		x		x	
Change_in_Drug_Days	Number of days between date of ID and date of FIRST change as a Change in ICS drug.	1 Year After ID	Numeric	10		x		x	
Change_in_Device_1st	Indicate if their first change in therapy was a change in device: 1 = Yes, 0 = No	1 Year After ID	Numeric	1		x			x
Change_in_Device_Days	Number of days between date of ID and	1 Year After ID	Numeric	10		x		x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
	date of FIRST change as a Change in Device.								
Add_on_Therapy_1st	Indicate if their first change in therapy was the addition of a LTRA or Theophylline: 1 = Yes, 0 = No	1 Year After ID	Numeric	1		x		x	
Add_on_Therapy_Days	Number of days between date of ID and date of FIRST change as the Add on of Therapy.	1 Year After ID	Numeric	10		x		x	
Increase_in_ICS	Indicate if change in therapy was an increase in their ICS. Please Note: A patient could have multiple changes: 1 = Yes, 0 = No	1 Year After ID	Numeric	1		x		x	
Change_in_Drug	Indicate if change in therapy was a change in their ICS drug type. Please Note: A patient could have multiple changes: 1 = Yes, 0 = No	1 Year After ID	Numeric	1		x		x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
Change_in_Device	Indicate if change in therapy was a change in device category ie BAI,MDI,DPI. Please Note: A patient could have multiple changes: 1 = Yes, 0 = No	1 Year After ID	Numeric	1		x		x	
Change_in_Device_Type	Indicate if patient changed device type ie Accuhaler to Clickhaler. 1 = Yes, 0 = No. Please Note: does not affect treatment success.	1 Year After ID	Numeric	1		x		x	
Add_on_Therapy	Indicate if change in therapy was the addition of a LTRA or Theophylline. Please Note: A patient could have multiple changes. 1 = Yes, 0 = No	1 Year After ID	Numeric	1		x		x	
Add_Seretide	Indicate if the addition of therapy was as a fixed combination inhaler Seretide. Please note: Patient could have multiple additional therapies. 1 = Yes, 0 = No	1 Year After ID	Numeric	1		x		x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
Add_Symbicort	Indicate if the addition of therapy was as a fixed combination inhaler Symbicort. Please note: Patient could have multiple additional therapies. 1 = Yes, 0 = No	1 Year After ID	Numeric	1		x		x	
Add_Fostair	Indicate if the addition of therapy was as a fixed combination inhaler Fostair. Please note: Patient could have multiple additional therapies. 1 = Yes, 0 = No	1 Year After ID	Numeric	1		x		x	
Add_LABA	Indicate if the addition of therapy was a separate LABA inhaler. Please note: Patient could have multiple additional therapies. - 1 = Yes, 0 = No	1 Year After ID	Numeric	1		x		x	
Add_LTRA	Indicate if the addition of therapy was as a leukatriene antagonist. Please note: Patient could have multiple	1 Year After ID	Numeric	1		x		x	

Variable_Name	Description	Period	Data Type	Length	Definition / Validation Rules	Data present in primary care database	Data present in hospital database	Data present in pharmacy database	Data present in test database
	additional therapies. 1 = Yes, 0 = No								
Add_THEO	Indicate if the addition of therapy was as a theophylline. Please note: Patient could have multiple additional therapies: 1 = Yes, 0 = No	1 Year After ID	Numeric	1		x		x	

ANNEX 2: EXAMPLE RESULTS TABLES

Please note that the following are only examples and numbers and categorisations reported below can change as appropriate to the data.

For binary logistic regression

Asthma Control	Treatment Group		Total
	A	B	
Controlled n (%)			
Uncontrolled n (%)			
Total n (%)			
Odds Ratio adjusted for baseline confounders * (95% CI)	1.00		

Table X: Summary Results for Asthma Control

*Adjusted for:

For Poisson/ Negative Binomial regression

Exacerbations (ATS Definition)	Treatment Group		Total
	A	B	
None n (%)			
1 n (%)			
2+ n (%)			
Total (n)			

Table X: Summary Results for Exacerbations (ATS Definition) (IPDI Matched Cohort)

p = 0.xxx (Conditional Logistic Regression)

Exacerbations (ATS Definition)	Treatment Group	
	A	B
Rate Ratio adjusted for baseline confounders* (95% CI)	1.00	

Table X: Exacerbation Rates (ATS Definition)

*Adjusted for:

For Ordinal Logistic regression

Average Daily SABA usage	Treatment Group		Total
	A	B	
1-100 mcg n (%)			
101-200 mcg n (%)			
201-400 mcg n (%)			
401-800 mcg n (%)			
801+ mcg n (%)			
Total n (%)			
Odds Ratio of a **higher** categorised SABA Dosage compared with a **lower** categorised dosage, adjusted for baseline confounders* (95% CI)	1.00		

Table X: Summary Results for Average Daily SABA usage

* Adjusted for:

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