Protocol: Validation of real-life asthma research endpoints

A Respiratory Research Group research initiative conducted in collaboration with Research in Real Life

CONTENTS

STUDY CONTEXT & APPROACH

AIM

The aim of this study is to validate a series of objective asthma control measures that have been used in published real-life respiratory research. The outcome measures (see **Appendix 1** for a list) will be compared and contrasted to patient-reported outcomes and/or gold-standard, validated asthma control tools and measures (as appropriate). Where possible, their validity, responsiveness and predictive value will also be assessed and a rank order of outcomes (and possibly hierarchical modelling) will be established to aid in appropriate outcome selection for future studies.

BACKGROUND

The study will be led by the Respiratory Effectiveness Group (REG) and will build on previous validation work that was presented at the 2011 European Respiratory Society Congress by Research in Real Life (RiRL) (see Appendix 2 to the study protocol).

The results of RiRL real-life respiratory studies have been published in leading respiratory journals, including: The New England Journal of Medicine , The *Journal of Allergy and Clinical Immunology*, *Respiratory Medicine* and *Clinical and Experimental Allergy*. Despite these publishing successes, however, their primary research papers often meet with challenges from peer reviewers who are unfamiliar with the described methods. Particularly problematic are real-life outcomes that refer to "asthma control," as they differ from the traditional, validated clinical tools (e.g. asthma control test [ACT], asthma control questionnaire [ACQ]). Outcomes in observational studies using primary care databases are limited to the recorded data, which usually do not include daily symptoms or spirometry results. Instead, real-life studies use proxy and composite measures to evaluate asthma diagnoses (e.g. indicative prescribing ± diagnostic read codes ± spirometric confirmation), exacerbations (e.g. prescriptions for short-term respiratory medications and hospitalisations or Accident & Emergency attendance for asthma to indicate fare-ups) and symptoms (e.g. prescriptions for short-acting beta agonists to indicate dependence medication for symptom relief). Two common reviewer concerns about the use of such proxies are: (i) whether the baseline and diagnostic data are reliable and complete, and (ii) whether the composite outcome measures are valid, i.e. they are accurate reflections of the clinical reality i.e. they are accurate reflections of the clinical reality. Usually these concerns implicitly assume (that the gold standard in outcome assessment are the measures used in prospective randomized controlled trial (RCTs), and thus request information regarding the association between real-life outcome assessments and RCT-used tools.

Further uncertainty in the robustness of real-life outcomes is introduced by inconsistent coding of events and omission of secondary care (asthma-related hospitalisations and Accident & Emergency attendance) or out-of-hours events within primary care records.

In the absence of a recognised gold standard set of validated outcome measures in real-life respiratory research, such comments will continue to be levelled and responding to them will continue to be challenging unless robust validation work is undertaken.

It would be beneficial for all involved (other researchers working in real-life respiratory research, journal publishers and reviewers) to be able to utilise, and refer to a standard set of real-life outcome measures that have been validated in terms of their relevance and responsiveness, as well as their ability to predict future risk, against gold standard endpoints used in clinical trials and against patient reported outcomes.

Not only would the establishment of a set of standard, real-life asthma outcomes help guide researchers and publishers, it would also help standardise real-life study designs across disparate research groups and help to set benchmarks for high quality study design.

METHODS

Literature Review

Appendix 3 details extracts from various groups who have previously undertaken validation work around some of the outcomes covered by this protocol. This literature provides context to our investigations and in some instances (e.g. the work around the short-acting beta agonist threshold associated with control / lack of control) reinforces our assumptions. However, while this protocol acknowledges that prior work, it will not assume those data to be correct, rather we will aim to undertake a series of independent validation activities.

Real-life data sources

Real-life asthma studies typically use clinical databases containing anonymised data extracted from patients' electronic medical records (EMRs). The EMRs (collected within primary care and/or secondary or tertiary care facilities, or healthcare insurers) are pooled and collated within an anonymised database.

Such databases tend to include objective data on: patient demographics; diagnostic data; prescribing data and healthcare resource utilisation data. These data can be used to test hypotheses and to carry out a variety of different analyses, such as comparative effectiveness analyses, safety evaluations and monitoring the real-life prescribing patterns.

Enhanced datasets – electronic medical records *and* patient-reported outcomes

This validation study will use data from the Optimum Patient Care Research Database (OPCRD) dataset.

The **OPCRD**, which comprises data captured through the Optimum Patient Care clinical service evaluation. Optimum Patient Care (OPC) is a not-for-profit organisation that offers free respiratory clinical evaluations for primary care practices. The clinical evaluation involves a review of (anonymised) EMRs and also responses to disease-specific questionnaires (see **Appendix 4** for a copy of OPC's asthma questionnaire). OPC evaluates the anonymous patient-level data (objective and subjective combined) to assess each patient's asthma control and risk and makes guideline-based recommendations for possible management changes, where appropriate. OPCRD contains all the anonymised data captured through the OPC service (see **Appendix 5** for a full data dictionary) and has been approved for clinical research use by the Trent Multicentre Research Ethics Committee (Trent MREC).

As a result of the extra patient-reported data fields contained within OPCRD, it is possible to assess objective outcome measures against subjective, patient-reported measures, and to evaluate gold standard measures, such as asthma control (as defined by GINA) against objective measures. OPCRD provides a unique and robust way to interrogate and validate the objective measures currently being used in real-life asthma studies.

RESEARCH TEAM

This study will be undertaken as a collaboration between the Respiratory Evaluation Group (REG) in collaboration with RiRL, and the research group will include members from both organisations, namely:

Lead Investigator – Richard Martin, National Jewish Health, Denver, Colorado, USA

REG Steering Committee Members:
David Price: University of Aberdeen, United Kingdom
Alex Dima: University of Amsterdam, The Netherlands
Alan Kaplan: Primary Care Physicians, Ontario, Canada
Gene Colice: Washington Hospital Center, Washington, DC, USA
Todor Popov: Medical University, Sofia, Bulgaria
Janet Holbrook: Professor of Epidemiology, John Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA
Emilio Pizzichini: Universidade Federal de Santa Catarina, Departamento de Clínica Médica, Brazil, Pulmonology
Nikos Papadopoulos: University of Athens, Greece
Guy Brusselle: Ghent University Hospital, Belgium
Helen Reddel: Woolcock Institute of Medical Research, Australia

RiRL Study Group Members:
Research Director (and REG member): Professor David Price, Professor of Primary Care Respiratory Medicine and Director of Research in Real Life
Data Analyst: Julie von Ziegenweidt

Statistics Team: Annie Burden (Senior Statistician), Vicky Thomas, Muzammil Ali
Medical Writer: Liz Hillyer

Respiratory Effectiveness Group

The Respiratory Effectiveness Group will be represented by its lead Steering Group, with Dr Richard Martin (Respiratory Physician and Chairman of the Department of Medicine at National Jewish Medical and Research Center, Denver, Colorado) assuming the responsibility of Principle Investigator.

REG Lead Working Group	
David Price, UK	Nikos Papadopoulos
Gene Colice, USA	Guy Brusselle, Belgium
Todor Popov, Bulgaria	Helen Reddel, Australia
Janet Holbrook, USA	Alex Dima, The Netherlands
Emilio Pizzichini, Brazil	

Alison Chisholm (REG Director, and writer of this protocol) will help in the project management of the study.

Research in Real Life

Research in Real Life have nominated the following team to work on this study:

Research Director (and REG member): Professor David Price, Professor of Primary Care Respiratory Medicine and Director of Research in Real Life

Data Analyst: Julie von Ziegenweidt

Statistics Team: Annie Burden (Senior Statistician), Vicky Thomas, Muzammil Ali

Medical Writer: Liz Hillyer

STUDY DESIGN

STUDY POPULATION

Inclusion criteria

Patients within the OPCRD dataset who:

(i) Either start, step-up or change maintenance ICS asthma therapy at an index prescription date (IPD) (i.e. the IPD for each eligible patient is the date at which they initiated, stepped-up or changed therapy[1])
(ii) Have ≥2 continuous years' practice data, including ≥1 year before the index prescription date and ≥1 year after the index prescription date
(iii) Have an asthma diagnostic code and/or receive ≥2 respiratory prescriptions in the year before IPD (baseline year) and ≥2 respiratory prescription in the year after IPD (outcome year) (i.e. ≥1 in addition to that prescribed at IPD)

[1] These patients would be expected to demonstrate a response to therapy, i.e. a change in asthma-control related endpoints between baseline and outcome

(iv) Aged 5–60 years

will be included in the study.

For the subset of patients where validation involves comparison with GINA control status or patient reported outcomes, the following alternative inclusion criteria will be applied:

(i) Have recorded questionnaire data at date of last extraction;
(ii) Have ≥1 year of continuous practice data before the index date;
(iii) Have an asthma diagnostic code and/or receive ≥2 respiratory prescriptions in the year before ID;
(iv) Are aged 5–60 years;

Exclusion criteria

(i) Diagnostic codes (Read codes) for chronic respiratory conditions other than asthma.
(ii) Maintenance oral steroids at any time during the baseline year.

Study period

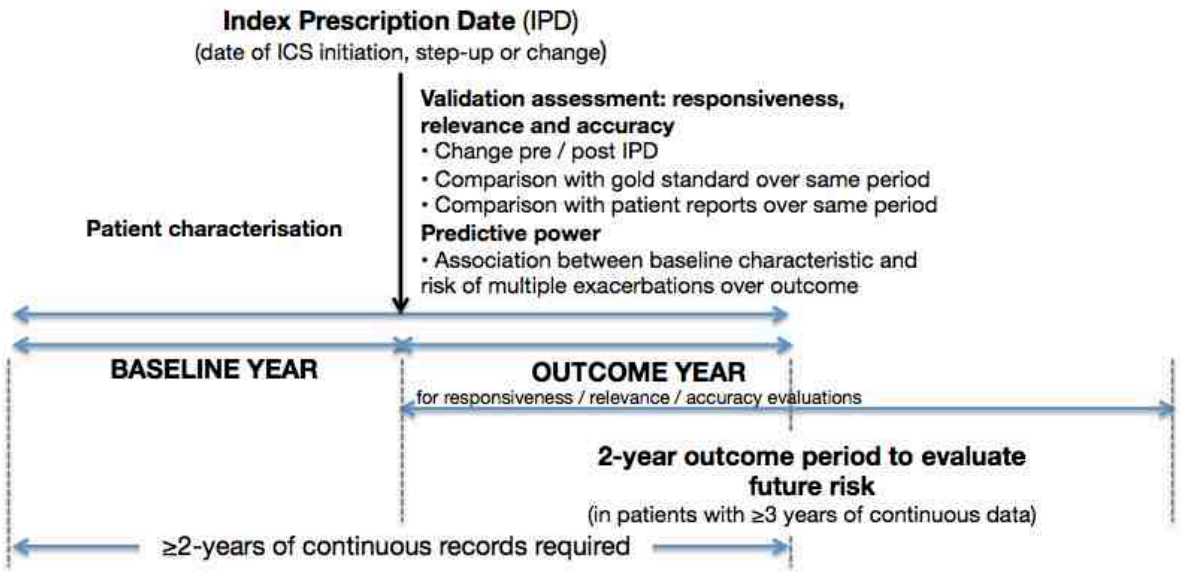
Responsiveness and valid:

The clinical validity of endpoints and their responsiveness will be evaluated by characterising patients over the 1-year baseline period immediately prior to IPD (i.e. date of initiation, step up or change of inhaled corticosteroid therapy) and evaluating any change in outcome in the 1-year period immediately after IPD. Objective real-life and gold standard measures will be compared over equivalent periods.

NB: An endpoint can be clinically valid without being responsive.

Future risk:
The predictive power of the objective outcomes will be evaluated using a range of statistical methods to explore whether they are associated with elevated risk of moderate-severe exacerbations in the future. “High risk” will be defined as ≥2 ATS/ERS-defined moderate-severe exacerbations in the following 1- and 2-year periods.

NB: An endpoint can be clinically valid without being predictive, i.e. not all endpoints will predict future exacerbations but can accurately reflect the clinical reality they are used to assess.



Where validation involves comparison with GINA control status or patient reported outcomes, the "Index Date" (ID) will be taken to be the date of the last data extraction from the practice by OPC. GINA control / patient reported outcomes will be assessed over the appropriate period immediately prior to ID using questionnaire data from the extraction and will be compared with routinely recorded medical data over the 1 year prior to extraction.

Figure illustrate this alternative design.

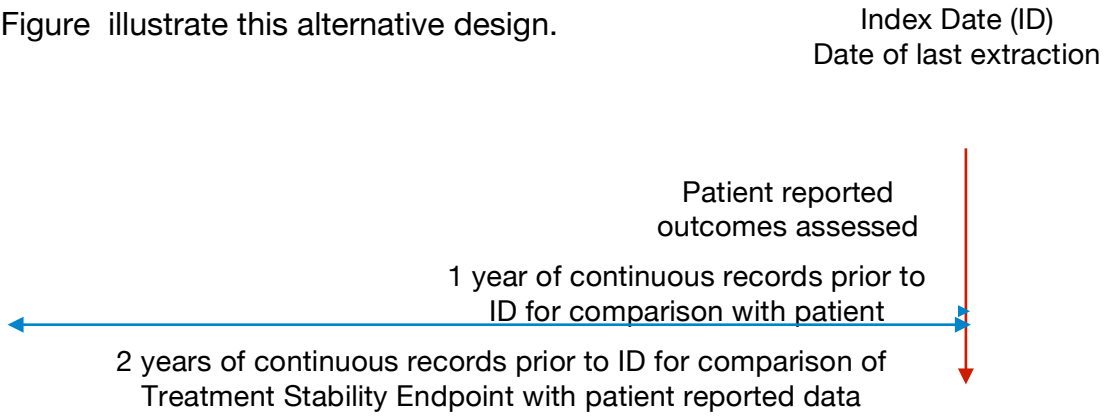


Figure 2: Alternative Study Design

RATIONALE AND APPROACH

This study aims to assess features of real-life study endpoints in terms of their:

(i) **Validity of measure:** assessment of how well a measure reflects a clinical reality of interest. As RCT-measures of control and exacerbations are often considered the gold standard means of measuring the clinical realitys (of

control and exacerbations) this study will compare real-life objective measures against validated RCT assessment tools e.g.:

- Control gold standard = Global Initiative for Asthma [GINA] control
- Gold standard moderate-severe exacerbations = (i) moderate-severe exacerbations as defined by the European Respiratory Society / American Thoracic Society (ERS/ATS) Taskforce and (ii) patient-reported exacerbations.

(ii) **Responsiveness of measure:** assessment of whether real-life endpoints respond to appropriate[2] therapeutic asthma interventions. NB. Not all valid endpoints will be responsive to guideline-recommended therapeutic changes (i.e. current guidelines may not produce notable changes in clinical practice; real-life outcome tools may inform improvement of current guidelines)

(iii) **Future risk prediction**: an assessment of whether endpoints used in real-life asthma studies are able (if appropriate) to predict future asthma risk (i.e. whose current status can be used to infer an increased / decreased risk of moderate-severe exacerbations over a later period of evaluation). NB not all endpoints will have predictive power as some outcomes are unrelated to exacerbations so would not be expected to future exacerbations

ENDPOINT VALIDATION

Validation of the following outcomes will be carried out:

(i) Control

a. Risk Domain Asthma Control (RDAC)
b. Overall control

RDAC and overall asthma control are expected to be highly correlated with GINA control and with asthma exacerbations (because RDAC defines control as lack of exacerbations).

(ii) Exacerbations

a. Severe exacerbation (based on ATS/ERS taskforce definition)
b. Physician-extended exacerbation definition (extension of the ATS/ERS taskforce definition informed by respiratory clinicians)

Exacerbations are expected to be (negatively) correlated to GINA control.

(iii) Therapeutic doses

Average reliever/rescue therapy usage (i.e. mean short-acting beta agonist [SABA] daily dosage)
Average reliever therapy usage is expected to be negatively correlated with

[2] Where appropriate is defined as guideline-recommended treatment options

GINA control as higher dependence on reliever therapy is likely to be related to greater symptoms and poorer disease control.

(iv) Controller-to-reliever ratio.

A larger controller to total controller-reliever ratio is expected to be correlated with GINA control as a higher ratio is associated with less use of reliever therapy and, hence, better symptom and disease control. However, the correlation with GINA control is not expected to be high because it depends not only on daily dose prescribed, but also on adherence to therapy.

(v) Medication compliance

A complex relationship between medication possession ratio and GINA control is expected with MPR at the high and low ends o the spectrum being associated with less-than-required and more-than-required use of maintenance therapy, suggesting both uncontrolled disease due to insufficient treatment (at the lower end of the spectrum) and due to difficult-to-control disease (At the higher end of the spectrum)

(vi) Treatment success (RDAC and no change or use of additional therapy)

Treatment stability is expected to be highly correlated to GINA control as the measure encompasses absence of exacerbations (as do measures of asthma control) and also absence of a change in therapy that may suggest prior therapy was inadequate or inappropriate.

(vii) Hospitalisations (inpatient admissions)

a. Asthma inpatient admissions
b. Lower respiratory inpatient admissions

As for exacerbations, hospitalisations are expected to be (negatively) correlated to GINA control as they are a marker of severe exacerbations

(viii) Oral Thrush

It is hypothesised that oral thrush may be higher in patients with poorer control and have higher medication dependence (i.e. who are prescribed higher doses of corticosteroids).

Full outcome definitions and evaluation specifics are detailed below.

Control

Definitions

a. Risk Domain Asthma Control (RDAC): absence of the following aspects of asthma risk during the outcome period:

(i) Asthma-related:[1] A&E attendance; Hospitalisation (in-patient admission); out of hours attendance[1], or out-patient department attendance
(ii) GP consultations for lower respiratory tract infections (LRTIs)
(iii) Prescriptions for acute courses of oral steroids

Failure to achieve RDAC: defined as all others.

b. Overall control: absence of asthma risk and impairment during the outcome period:

(i) Asthma-related: A&E attendance; Hospitalisations (inpatient admissions); out of hours attendance, or out-patient department attendance
(ii) GP consultations for LRTIs
(iii) Prescriptions for acute courses of oral steroids
(iv) Average daily dose[1] of:
  a. **UK**: ≤200mcg salbutamol / ≤500mcg terbutaline
  b. USA: ≤180mcg salbutamol / albuterol or ≤500mcg terbutaline

Failure to achieve overall control: defined as all others.

Validation evaluations

Validity – accurate reflection of the clinical reality
Comparison vs GINA[3]

(i) Evaluate whether there is a change in "RDAC" and "Overall Control" status between the baseline and outcome periods.

(ii) Evaluate the percentage of patients meeting the "RDAC" and "Overall Control" outcomes who meet:
  a. GINA-defined control
  b. GINA-defined partial control
  c. GINA-defined control or partial control

(iii) Evaluate the relationship between the disaggregated components of RDAC and overall control and the different GINA control categories (total control, partial control, total+partial control) using univariate and multivariate analyses to explore the most meaningful way of combining variables to best reflect true (GINA-defined) control.

[3] This will assess how well real-life measures of control reflect RCT-measures of control (it is often assumed that RCT measures are the gold standard)

GINA control will be assessed over a 1-week period. For this analysis, the date of questionnaire completion (GINA control assessment) will be taken as the Index Date (ID); and RDAC/OAC will be assessed over the 1-year period prior to ID. The precise time between RDAC/OAC control and GINA questionnaires completion will not be known exactly, but will be within one-month (likely 1–2 weeks) of each other.

GINA levels of asthma control

GINA Control – the GOLD Standard: *"The assessment of asthma control should include control of the clinical manifestations and control of the expected risk to the patient such as exacerbations, accelerated decline in lung function and side-effects of treatment. In general, the achievement of good clinical control of asthma leads to reduced risk of exacerbations."*[7]

A. Assessment of current clinical control (preferably over 4 weeks)			
Characteristic	Controlled (all of the following)	Partly controlled (any present in any week)	Uncontrolled
Daytime symptoms	None (≤2 per week)	More than twice per week	≥3 or more features of partly controlled asthma*†
Limitation of activities	None	Any	
Nocturnal symptoms	None	Any	
Need for rescue / "reliever" mediation	None (≤2 per week)	>2 per week	
Lung function (PEF or FEV_1)‡	Normal	<80% predicted or personal best (if known)	

*Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate
†By definition, an exacerbation in any week makes that an uncontrolled asthma week
‡Without administration of bronchodilator
Lung function is not a reliable test for children 5 years and younger

B. Assessment of Future Risk (risk of exacerbations, instability, rapid decline in lung function, side-effects)
Features that are associated with increased risk of adverse events in the future include: Poor clinical control, frequent exacerbations in the past year*, ever admission to critical care for asthma, low FEV_1, exposure to cigarette smoke, high dose medications

(From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2012. Available from: http://www.ginasthma.org/)

Validity of measure:

(i) Plot the SABA usage for both the patient subpopulations achieving vs not achieving:

a. RDAC
b. GINA-defined control
c. GINA-defined partial control
d. GINA-defined control+partial control

Using a receiver-operating characteristic (ROC) curve, identify the most appropriate SABA usage threshold for identifying asthma impairment / symptoms and for use within the "overall control" definition..

Given previously observed differences in routine SABA use among patients of different smoking status (see **Appendix 6),** ROCs will be produced for all asthma patients, and also for the different smoking subgroups within the population, i.e.:

a. Current smokers
b. Ex-smokers
c. Non-smokers

(ii) Examine the effect on the confidence intervals for "RDAC" and "Overall Control" of excluding and including the disaggregate variable of "GP consultations for LRTIs". Examine whether inclusion of this component increases or decreases the power.

Responsiveness of measure:

Evaluate whether there is a change in "RDAC" and "Overall Control" status between the baseline and outcome periods. Asthma control status would be expected to change (improve) with a change in therapy (initiation / stepping-up). For this analysis, the initiation and step-up cohorts will be used.

Future risk prediction:

(i) The association between "RDAC" and "Overall Control" in the year prior to index date and moderate-severe exacerbations (ATS/ERS-defined) in the subsequent 1-year period and (where data are available) 2-year period will be evaluated, making suitable adjustments for treatment changes during the outcome periods. The predictive value of each disaggregated component of moderate-severe exacerbations risk will also be assessed in univariate and multivariate analyses.

(ii) The association between the nature of **GP consultations** (and coding) over a baseline year and severe exacerbation rate in the following 1 and 2-year periods will be evaluated by considering the following types of GP consultations:

a. Any
b. Asthma
c. Lower respiratory (including asthma)
d. Consultations resulting in a prescription for oral steroids
e. Consultations resulting in a prescription for antibiotics for a LRTI
f. Consultations resulting in an oral steroids prescription or antibiotics for a LRTI.

Exacerbations

The ATS/ERS Taskforce Guidelines define exacerbations (in clinical practice) as events characterized by a change from the patient's previous status:[4]

- Severe asthma exacerbations are defined as events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma.
- Moderate asthma exacerbations are defined as events that are troublesome to the patient, and that prompt a need for a change in treatment, but that are not severe. These events are clinically identified by being outside the patient's usual range of day-to-day asthma variation.

Although several studies have reported ''mild'' exacerbations, the Task Force considered that these episodes were only just outside the normal range of variation for the individual patient and that with present methods of analysis, they could not be distinguished from transient loss of asthma control. Hence no definition of a "mild" exacerbation is offered.

Not only do exacerbations represent a transient worsening of asthma symptoms and increased asthma impairment, but they are associated with sustained damage to the lung tissue. Prior exacerbations are also an independent predictor of future exacerbations in asthma.[5]

[4] Reddel H, Taylor RD, Bateman ED, et al. An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations: Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice. Available online at: http://www.thoracic.org/statements/resources/allergy-asthma/ats-ers-asthma-control-and-exacerbations.pdf (last accessed 14 August 2013)

[5] Miller MK, Lee JH, Miller DP, Wenzel SE, TENOR Study Group Recent asthma exacerbations: a key predictor of future exacerbations. Respir Med. 2007;101:481-9.

Definitions

a. Severe exacerbation: based on ATS/ERS taskforce definition:

(i) Asthma-related:
   a. Hospitalisations (inpatient admissions) OR
   b. A&E attendance OR

(ii) Use of acute oral steroids.

b. Physician-extended exacerbation definition: extension of the ATS/ERS taskforce definition of a severe exacerbation bases on clinician guidance that exacerbations are often recorded as lower respiratory tract infections:

(i) Asthma-related:
   a. Hospitalisations (inpatient admissions) OR
   b. A&E attendance OR
   c. Out of hours attendance OR

(ii) GP consultations for lower respiratory related tract infections

(iii) Use of acute oral steroids.

Validation evaluations

Validity of measure:

(i) Evaluate whether there is a change in number of moderate-severe exacerbations during the baseline and outcome years.

(ii) Examine the relationship between components of real-life exacerbations

(iii) Compare and contrast the rate of recorded objective and patient-reported exacerbations

*Patient-reported exacerbation will be defined as a positive response to any of the following questions in the OPC questionnaire (see **Appendix 4** for the full questionnaire):

Did you, in the last year, have:
(a) Any courses of oral steroids for worsening asthma?
(b) Time off work/school because of asthma?
(c) Hospitalisations (inpatient admissions) due to asthma?

(iv) Examine whether including / excluding the disaggregate variable: "GP consultations for LRTIs" increases or decreases the confidence interval and positively / negatively affects the power.

Responsiveness of measure:

Evaluate whether there is a change in number of moderate-severe exacerbations during the baseline and outcome years.

Exacerbation rates would be expected to change (improve) with a change in therapy (initiation / stepping-up / switching of ICS therapy). For this analysis, the initiation, step-up and switch cohorts will be used. Baseline and outcome exacerbation rates

(ATS/ERS-defined and Physician defined) will be compared using Wilcoxon Signed-rank tests for paired data and p values reported.

Future risk prediction

(i) The association between incidence of each disaggregated component of the objective exacerbation outcomes over a 1-year baseline period and severe exacerbation risk in the 1- and 2-year period post IPD will be evaluated. Identify which disaggregate component(s) of exacerbations are key exacerbation drivers (for both objective and patient-reported exacerbations), e.g. is secondary care healthcare utilisation (hospitalisations and A&E attendance) more / less predictive of future exacerbations than oral steroids?

(ii) Use each of the following definitions to predict frequency of itself and each other in the subsequent 1- and 2-year periods:
   a. Patient-reported exacerbations
   b. ATS/ERS objective measure
   c. Extended ATS/ERS definition (based on clinical practice insights)

Therapeutic doses

Definitions

a. Average SABA daily dose, defined as: Sum of total days covered by prescriptions x daily dose / number of days in the year

b. Average ICS daily dose, defined as: Total ICS prescribed over the course of the year (i.e. sum of total drug contained within each prescribed inhaler) / number of days in the year

Validation evaluations

Validity of measure:

Interaction of SABA usage with control measure

(i) Evaluate the average SABA daily dosage in baseline and outcome years and identify:
   a. Any associations between SABA daily dosage and control status (RDAC and GINA-defined);
   b. Any associations between SABA daily dosage and *change in* control status (RDAC).

(ii) Identify the lower limit, median and upper limit of the SABA daily dosage within each GINA control category.

Responsiveness of measure:

Evaluate the change in SABA daily dosage between baseline and outcome.

For this analysis, the initiation, step-up and switch cohorts will be used.

Changes in dosages from the baseline to outcome period will be calculated and summary statistics (sample size; mean (SD); median (IQR); range (minimum, maximum)) reported.

Baseline and outcome dosages will be compared using Wilcoxon Signed-rank tests for paired data and p values reported.

Future risk prediction:

(i) Evaluate the association between **average daily SABA dosage** over the baseline period and moderate-severe exacerbations in the following 1 and (where data are available) 2-year periods (split by SABA dosage category as best characterises the baseline usage of the population under evaluation e.g., 0–200mg; 201–400mcg; 401–500mcg…)

Adherence

Medication possession ratio is often used as a proxy measure of adherence in observational studies using clinical or administrative datasets. It is truly a marker of medication coverage over a specified outcome period and is dictated by the number of prescriptions issued (or preferably collected) over an outcome period of interest. In the UK, MPR driven by how often a patient contacts their primary care clinician seeking additional medication. As such it is a proxy maker of medication usage and, therefore, adherence. However, prescriptions issued do not necessarily equate to prescriptions collected (although in the UK these are closely related) and prescriptions collected does not equate to medication actually consumed.

Moreover, the relationship between MPR and disease control is complex, as (in routine care) patients often self-titrate – increasing their medication usage during periods of poorly controlled disease and decreasing it during periods of well controlled disease.

Definition

Medication possession ratio (MPR), defined as: total days within the year for which collected prescriptions would provide therapeutic coverage as a percentage of the total number of days in 1 year (cut-off: <0.8 / ≥0.8)

Validation evaluation(s)

Validity of measure

Association between real-life study objective endpoint (medication possession ratio) and patient-reported adherence

(i) Evaluate the association between MPR and patient-reported adherence categories and the lower limit, median and upper limit of MPR for each patient-reported adherence category, where patient-reported adherence categories are split as:

1. I take it ever day
2. I take it some days but others I do not
3. I used to take it but now I do not;
4. I take it only when I have symptoms; I never take it

(ii) Evaluate any association between patient-perceived need for maintenance medication and MPR, where perceived need is evaluated on a 5-category scale of:

1. Strong agreement
2. Agreement
3. Uncertainty
4. Disagreement
5. Strong disagreement

To the question: "I need to take my inhaler regularly for my asthma to be well controlled"

(iii) Evaluate the duration of different types of licensed devices and explore any possible interaction between duration of inhaler and MPR with prescribed therapy, e.g. MPR (a proxy for adherence) may be higher in patients who do not need to collect new devices as frequently – a "false" reflection of effectiveness, albeit a possible real-life effect of formulation choice.

Responsiveness of measure

(i) Evaluate the mean increase / decrease in MPR over 1 year before and after a change in medication:
   a. ICS step up (≥50% increase in dose)
   b. ICS switch (<50% change in effective ICS dose)

The change in MPR between the baseline and outcome years will be evaluated and summary statistics reported.

Future risk prediction:

(i) The association between MPR in the year prior to index date and moderate-severe exacerbations (ATS/ERS-defined) in the subsequent 1-year period and (where data are available) 2-year period will be evaluated, making suitable adjustments for treatment changes during the outcome periods (consider both categorical [<0.8; ≥0.8] and continuous relationships).

Controller-to-reliever ratio

Definition
Controller-to-reliever ratio defined as: Units of Controllers / (Units of Controllers + relievers).

For the purposes of this validation study, "Controllers" are inhaled corticosteroids (including fixed combination ICS/LABA) and LTRA; "Relievers" are SABA. For ICS a unit is taken to be one inhaler; for LTRA a unit is one prescription. LABA is not included as a controller (as the number of "controllers" would be distorted by fixed combination /separate inhalers). SABA is the only reliever included in the analysis; a "unit" is one inhaler.

Validation evaluation(s)

Validity of measure:

(i) The association between controller-to-reliever ratio and gold standard asthma control (i.e. GINA-defined control status – controlled; partially controlled; uncontrolled) will be evaluated. Controller-to-reliever ratio will be evaluated as:
   a. A continuous variable;
   b. A categorical variable (0.5 cut-off).

(ii) The lower limit, median and upper limit of the controller-to-reliever ratio for each GINA control category will be explored.

(iii) The impact of treatment duration for different licensed maintenance therapy options on the controller-to-reliever ratio will be explored, including any interaction between duration of controller therapy and recorded controller-to-reliever ratio.

To identify associations between the controller-to-reliever ratio and GINA-defined control status, the date of questionnaire completion (GINA control assessment) will be taken as the Index Date (ID) and the controller-to-reliever ratio will be assessed over the 1 year period prior to ID.

Responsiveness of measure:

The change in controller-to-reliever ratio between the baseline and outcome years will be evaluated. For this analysis, the step-up and switch cohorts will be used. Baseline and outcome controller-to-reliever ratios will be compared as:
   a. A continuous variable
   b. A categorical variable (0.5 cut-off)

Future risk prediction:

(i) The association between **controller-to-reliever ratio** in the year prior to index date and moderate-severe exacerbations (ATS/ERS-defined) in the subsequent

1-year period and (where data are available) 2-year period will be evaluated, making suitable adjustments for treatment changes during the outcome periods (consider both categorical [<0.5; ≥0.5] and continuous relationships).

Treatment stability

Treatment stability, as defined here, is a composite measure primarily combining RDAC (and absence of exacerbations) and absence of an increase in therapy. This measure extends the RDAC measure by including "therapy increase" based on the hypothesis that a substantial escalation of therapy (defined as at least a 50% increase in dose of existing therapy, or a new initiation of additional therapy) may be a marker of suboptimum asthma control and a reflection of a clinician's decision to to increase therapeutic management to improve control.

It may be affected by other drivers, although excluding a change in drug or device from the definition of therapy change seeks to ensure that the decision to change therapy is unlikely to be driven by cost arguments and to be more likely to be based on perceived clinical need.

Definitions

a. Treatment stablity is defined as:

(i) RDAC (see earlier definition)

(ii) No additional or change in therapy during the outcome period, where change or additional therapy is any of:
   a. Increased dose of ICS (≥50% increase)
   b. Use of additional therapy long-acting bronchodilator (LABA), theophylline, leukotreine receptor antagonists (LTRAs).

Validation evaluation(s)

Validity of measure

(i) The association between treatment success with gold standard control categories will be evaluated:
   a. GINA-defined control
   b. GINA-defined partial control
   c. GINA-defined control + partial control

   The treatment success definition that most closely reflects GINA control classifications will be identified.

For this analysis, the date of questionnaire completion (GINA control assessment) will be taken as the Index Date (ID); and Treatment Stability will be assessed over the 1 year period prior to ID for a sub-group of patients with 2 years of data prior to ID (so that changes in therapy during the 1 year prior to ID can be assessed).

Responsiveness & Future risk prediction

Treatment stability is evaluated in the post index period only, thus no change in treatment stability or predictive power of the measure can be assessed between baseline and outcome period in this study.

Hospitalisations

Hospitalisations coded for asthma, or asthma-related conditions, have been assumed in past observational study work to be a maker of severe exacerbations. As previously defined, the ATS/ERS Taskforce Guidelines define severe exacerbations as:[6]

- events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma.

Definitions

a. Asthma hospitalisations (inpatient admissions)

(i) **Definite**: Inpatient admissions coded with an asthma read code

(ii) **Definite + Probable**: Inpatient admissions with an asthma read code occurring within a 7-day window (either side of the admission date) of an asthma read code

b. Lower respiratory hospitalisations (inpatient admissions)

(i) **Definite**: Inpatient admissions coded with a lower respiratory code

(ii) **Definite + Probable**: Inpatient admissions with an lower respiratory read code occurring within a 7-day window (either side of the admission date) of an asthma read code

Validation evaluation(s)

Validity of measure

(i) To evaluate the extent to which the inpatient admissions records reflect:
   a. Patient-reported hospitalisations
   b. Hospital episode statistics (HES) coded for:
      • Asthma
      • Lower respiratory complaints.

For the comparison with patient-reported hospitalisations, the date of questionnaire completion will be taken as the Index Date (ID); and hospitalisations will be assessed over the 1-year period prior to ID.

[6] Reddel H, Taylor RD, Bateman ED, et al. An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations: Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice. Available online at: http://www.thoracic.org/statements/resources/allergy-asthma/ats-ers-asthma-control-and-exacerbations.pdf (last accessed 14 August 2013)

For the comparison with HES data, sub-groups of the initiation, step-up and switch cohorts will be used. These sub-groups will consist of patients for whom HES data are available during the 1-year outcome period.

Responsiveness of measure

The number, and change, in inpatient admissions between the baseline and outcome years will be evaluated.

Hospitalisation rates would be expected to change (improve) with a change in therapy (initiation / stepping-up / switching of ICS therapy). For this analysis, the initiation, step-up and switch cohorts will be used.

Future risk prediction:

The association between **inpatient admissions (each definition)** in the year prior to index date and moderate-severe exacerbations (ATS/ERS-defined) in the subsequent 1-year period and (where data are available) 2-year period will be evaluated.

Oral Thrush

In past observational study work, prescriptions for oral thrush have been interpreted as a marker of potential side-effects of excessive oropharyngeal deposition of inhaled corticosteroid therapy.

Definition

Oral thrush is defined in two ways:

Definition 1:

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

Definition 2:

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

Validation evaluation(s)

Validity of measure:

The proportion of patients for whom at least one course of oral thrush medication &/or a coded diagnosis is objectively recorded will be compared with the proportion

of patients reporting (via questionnaire) at least one case of oral thrush over the same time period. For this analysis, the date of questionnaire completion will be taken as the Index Date (ID); and incidence of oral thrush will be assessed over the 1 year period prior to ID.

Responsiveness of measure:

The incidence of oral thrush in the baseline and outcome years will be evaluated and compared.

Incidence of oral thrush may be expected to increase with an increase in ICS use. For this analysis, the initiation, step-up and switch cohorts will be used.

Future risk prediction:

Oral thrush is not expected to be predictive of future exacerbation risk; no risk prediction analysis will be conducted.

Statistical analysis

A full statistical analysis plan will be developed based on the outline of this study protocol.

Statistical analysis

All statistical analyses will be carried out using SAS v9.3, SPSS v20 and EXCEL 2007. The statistical methods that will be used, will include (as appropriate for the particular analysis under consideration):

(i) **Poisson Regression models:** will be used to determine predictors of future risk in terms of severe exacerbation rates over subsequent 1 & 2 years.
(ii) **Ordinal logistic regression models**: will be used when annual exacerbations are categorised 0,1 and ≥2.
(iii) **The Somers' d statistics**: will be used to assess the association between pairs of variables (such as risk domain asthma control [see later for definition] and control, as defined by GINA).
(iv) **Cohen's Kappa Coefficient:** will be used to assess inter-rater agreement of measures such as exacerbations identified through objective medical records & patient-reported exacerbations (see later for definitions).
(v) **Receiver Operating Characteristics (ROC) curves**: will be constructed in EXCEL 2007 using SABA threshold levels increasing in appropriate increments, to be informed by the data (e.g. 50mcg/day intervals).
(vi) Other analyses will use summary statistics: **Kruskal Wallis test** / **Chi Square test**.

APPENDICES

Appendix 1: Objective Outcome Summary

1. Control

(1a) Risk Domain Asthma Control (RDAC): absence of the following aspects of asthma risk during the outcome period:

(i) Asthma-related:[7] A&E attendance; Hospitalisation (in-patient admission); out of hours attendance[8], or out-patient department attendance
(ii) GP consultations for lower respiratory tract infections (LRTIs)
(iii) Prescriptions for acute courses of oral steroids

Failure to achieve RDAC: defined as all others.

(1b) Overall control: absence of the following aspects of asthma risk and impairment during the outcome period:

(i) Asthma-related: A&E attendance; Hospitalisations (inpatient admissions); out of hours attendance, or out-patient department attendance
(ii) GP consultations for LRTIs
(iii) Prescriptions for acute courses of oral steroids
(iv) Average daily dose[9] of:
   a. **UK**: ≤200mcg salbutamol / ≤500mcg terbutaline
   b. **USA**: ≤180mcg salbutamol / albuterol or ≤500mcg terbutaline

Failure to achieve overall control: defined as all others.

2. Exacerbations

(2a) Severe exacerbation: based on ATS/ERS taskforce definition:

(i) Asthma-related:
   a. Hospitalisations (inpatient admissions) OR
   b. A&E attendance OR
(ii) Use of acute oral steroids.

(2b) Physician-extended exacerbation definition: extension of the ATS/ERS taskforce definition of a severe exacerbation bases on clinician guidance that exacerbations are often recorded as lower respiratory tract infections

(i) Asthma-related:
   a. Hospitalisations (inpatient admissions) OR

[7] Asthma-related will be defined as all events coded with a lower respiratory code (including asthma)
[8] Note, "attendance" excludes virtual or phone-based healthcare interactions
[9] Taken rather than prescribed

b. A&E attendance OR
c. Out of hours attendance OR

(ii) GP consultations for lower respiratory related tract infections
(iii) Use of acute oral steroids.

(3a) Average SABA daily dose, defined as: (Number of days duration of each prescription prescribed throughout the year x daily dose) / number of days in the year (365)

(3b) Average ICS daily dose, defined as: Total ICS prescribed over the course of the year (i.e. total drug contained within each prescribed inhaler) / number of days in the year (365)

4. Compliance

Medication possession ratio, defined as: total days within the year for which collected prescriptions would provide therapeutic coverage as a percentage of the total number of days in one year (cut-off: <0.8 / ≥0.8)

5. Controller-to-reliever ratio

Defined as: Units of Controllers / (Units of Controllers + relievers)

6. Treatment success

(6a) Treatment success (irrespective of change in treatment cost associated with the treatment change) defined as:

(i) RDAC (see Appendix 1, item 1a for definition)
(ii) No additional or change in therapy during the outcome period, where change or additional therapy is any of:
a. Increased dose of ICS (≥50% increase)
b. Change in ICS
c. Change in delivery device
d. Use of additional therapy long-acting bronchodilator (LABA), theophylline, leukotriene receptor antagonists (LTRAs).

(6b) Treatment success (excluding treatment changes associated with a cost saving) defined as:[10]

(i) RDAC (see Appendix 1, item 1a for definition)
(ii) No additional or change in therapy during the outcome period, where change or additional therapy is any of:
a. Increased dose of ICS (≥50% increase)
b. Use of additional therapy (e.g. use of the following in patients receiving ICS ± short-acting bronchodilator at the index date: long-acting bronchodilator [LABA], theophylline, leukotriene receptor antagonists [LTRAs]).

[10] The rationale for this outcome is that some treatment changes are made to reduce treatment costs rather than being a reflection of sub-optimal management

7. Hospitalisations

(7a) Asthma hospitalisations (inpatient admissions)

(i) **Definite**: Inpatient admissions coded with an asthma read code
(ii) **Definite + Probable**: Inpatient admissions with an asthma read code occurring within a 7-day window (either side of the admission date) of an asthma read code

(7b) Lower respiratory hospitalisations (inpatient admissions)

(i) **Definite**: Inpatient admissions coded with a lower respiratory code
(ii) **Definite + Probable**: Inpatient admissions with an lower respiratory read code occurring within a 7-day window (either side of the admission date) of an asthma read code

8. Oral Thrush

An incidence of oral thrush is defined as: a topical oral anti-fungal prescription and / or a recorded *oral candidiasis* code.

Appendix 2: RiRL validation poster presented at the 2011 ERS

Composite measures of asthma control in real-life comparative effectiveness studies

POSTER #: P3772

D. Price,[1,2] R. Martin,[3] G. Colice,[4] P. Dorinsky,[5] A. Chisholm,[2] J. von Ziegenweidt,[2] A. Burden,[2] P. Polos,[6] L. Hillyer,[2] N. Roche[7]

[1] Centre of Academic Primary Care, University of Aberdeen, UK; [2] Research in Real Life, Norwich, UK; [3] National Jewish Health, Denver, USA; [4] Washington Hospital Center and George Washington University School of Medicine, Washington, DC, USA; [5] Teva Pharmaceuticals, Horsham, PA, USA; [6] i3 Research, USA; [7] Hotel-Dieu, Paris; USA

BACKGROUND

- Real-world studies allow evaluation of treatment effectiveness and prescribing patterns in everyday clinical practice.
- Real-world observational studies offer good external validity, but have less internal validity than RCTs.
- Confidence in real-life studies and their outcomes will grow through:
  - Use of relevant endpoints – those that respond to effective interventions
  - Validation of objective composite variables.
  - Consistent findings across a range of measures.

OBJECTIVE

- In a real-world relative effectiveness study of fluticasone propionate (FP) and extrafine hydrofluoro-alkane beclometasone dipropionate (EF HFA-BDP) in asthma patients initiating or increasing ICS therapy:
  1) Compare consistency of composite endpoints
  2) Validate the relevance of the endpoints

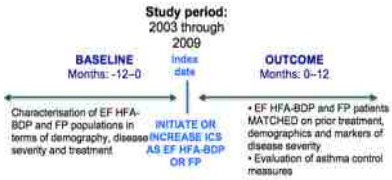
METHODS

- A retrospective, observational study using a clinical database comprising US health insurance claims – the **Ingenix Normative Healthcare Information Database**.

INCLUSION CRITERIA	
• **Age:** 5–80 years (and negative smoking history for patients ≥60 years)	• **Patient record:** continuous data available for 12 months prior to, and post index date
• **Evidence of asthma**: – diagnostic code for asthma in the database AND/OR – ≥2 asthma prescriptions in the outcome year	• **Known index date prescription**: date of initiation or step-up in ICS dose as FP MDI or EF HFA-BDP MDI

- Patients were MATCHED on baseline demography and disease severity: QVAR:FP 1:3 for the initiation cohort; 1:2 for the increase cohort.

MATCHING CATEGORIES	Initiation	Increase
Sex	✔	✔
Age (± 1 year (age ≤ 5 years); ± 3 years [age 6-12 years]; ± 5 years [age > 13 years])	✔	✔
SABA dosage	✔	✔
Number of oral steroid prescriptions	✔	✔
ICS daily dosing category (total claimed annual dose / 365 days)	X	✔
Asthma consultations not resulting in oral steroid prescription	✔	✔



- Unmatched dataset was used to compare range of single & composite baseline variables as predictors of outcome **Exacerbations**, **Hospitalisations** & **SABA usage** in univariate models to assess the validity of composite variables. OR/RRs, CIs and model-fit statistics were compared.
- **STATISTICS:**
- Descriptive statistics were used to compare baseline clinical profiles.
- Conditional logistic regression was used to compare asthma control status
- Conditional Poisson regression was used to compare differences in exacerbation rates, adjusting for any residual confounding.
- **Endpoint validity** was examined in **ICS increase patients only** to ensure **consistency of baseline data**.
  - "Valid endpoints" were those that responded to effective treatment; "valid baseline variables" predicted objective outcome measures.

METHODS (contined)

Co-Primary Outcomes (continued)…

- ***Severe Exacerbations***:
1) Unscheduled hospital admission or ER attendance for asthma, OR
2) Prescription for an acute course of oral corticosteroids.
Rationale: *ATS/ERS definition of severe exacerbations[1]*
- ***Asthma control:***
1) No severe exacerbations, and
2) No outpatient visits for asthma, and
3) No consultation, hospital admission, or ER attendance for a lower respiratory tract infection (LRTI) requiring antibiotics, and
4) No hospital admission or ER attendance for a lower respiratory reason.
Rationale*: Endpoint reflects the ATS/ERS definition[1] of severe exacerbations with additional components considered (by a group of UK practitioners and the study scientific committee) to be potentially indicative of sub-optimal asthma control (see components 2–4, above)*
- ***Asthma control sensitivity analysis: Asthma control + SABA:***
1)– 4) as above, plus
5) Average daily prescribed dose of salbutamol / albuterol ≤180mcg or terbutaline ≤500mcg.
Rationale*: Asthma control (above) with minimum SABA usage taken as a proxy for symptom control*

Secondary Outcomes

- ***Asthma control + no increase in therapy:***
1) – 4) as above plus
5) No increase in ICS dose or use of additional therapy (i.e. long-acting beta agonist; leukotriene receptor antagonists, theophylline).
Rationale*: Asthma control (above) with no therapy increase taken to be a proxy for achievement of effective asthma control with existing regimen*
- ***Controller-to-reliever ratio ≥0.5**:*** Units of Controllers / (Units of Controllers + Relievers).
Rationale*: A higher controller-to-reliever ratio (≥0.5) is significantly related to:[2,3]*
•Improved asthma-related quality of life,
•Better disease control
•Reduced symptoms.
- ***Mean ICS dose during outcome year:*** calculated from total ICS refills / 365 days.
Rationale: *provides insight into the true dose taken (claimed) rather than prescribed allowing association of outcomes with an approximate ICS dose.*
- ***Medication Prescription ratio***:*** 100% X (Number of days supply of ICS / 365 days)
Rationale: *a measure of adherence. In line with previous asthma studies, the MPR was categorised as a dichoto-mous variable: <80% (non-adherent), ≥80% (adherent).*

"Controllers" includes: ICS, ICS/LABA (1 unit = 1 x inhaler) and LTRA (1 unit =1xprescription); "Relievers" were SABA (1 unit=1xinhaler) ;"The numerator is truncated at 365 if greater than 365.

RESULTS

Endpoint Validation

	Outcome		
Baseline Predictors	Exacerbations (RR)	LR Hospital'ns (RR)	SABA Dosage (OR)
Asthma Control + SABA	2.12 [1.84-2.44]	2.34 [1.91-2.86]	2.14 [1.92-2.38]
Acute Oral Steroids	2.75 [2.47-3.07]	1.91 [1.66-2.19]	1.11 [1.00-1.23]
LR Hospitalisations	2.02 [1.79-2.26]	3.61 [3.15-4.13]	1.25 [1.12-1.40]
SABA Dosage	1.29 [1.15-1.45]	1.38 [1.19-1.59]	4.57 [4.08-5.13]

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1. Reddel HK, et al. *Am J Respir Crit Care Med. 2009; 180: 59-99*
2. Broder MS, et al. Ratio of Controller to Total Asthma Medications: Determinants of the Measure. *Am J Manag Care.* 2010;16(3):170-178.
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RESULTS (continued)

INITIATION	EF HFA-BDP (n=3633)	FP (n=10899)
Asthma control – YES n(%)	2008 (55.3)	5941 (54.5)
Achieved asthma control + SABA – YES n(%)	1403 (38.6)	3645 (33.4)
No severe exacerbations n(%)	2599 (71.5)	7756 (71.2)
Asthma control + no increase in therapy – YES n(%)	1575 (43.4)	4635 (42.5)
Controller–reliever ratio ≥0.5 n(%)	2588 (71.2)	7131 (65.4)
MPR ≥80% n(%)	281 (7.7)	984 (9.0)
Outcome year ICS dose (µg/d) Median (IQR)	44 (22, 88)	72 (36, 159)

Numbers in teal indicate P≤0.05

- Asthma control ± no increase in therapy were similar across measures and treatment groups.
- Significantly more EF HFA-BDP patients achieved Asthma control +SABA than FP patients, reinforced by the significantly higher percentage of EF HFA-BDP patients meeting the high controller-to-reliever ratio.
- On initiation, EF HFA-BDP was prescribed at less than half the daily dose of FP: median (IQR), EF HFA-BDP: 160 (160,320) µg/d versus 440 (176,440) µg/d, respectively). During outcome year, the mean daily ICS dose was ~1:4 of that prescribed at initiation for EF HFA-BDP and ~1:6 that prescribed at initiation for FP reflecting lower adherence among FP patients than EF HFA-BDP patients, as corroborated by the MPR.

INCREASE	EF HFA-BDP (n=316)	FP (n=632)
Asthma control – YES n(%)	171 (54.1)	333 (52.7)
Achieved asthma control + SABA – YES n(%)	115 (36.4)	204 (32.3)
No severe exacerbations n(%)	225 (71.2)	454 (71.8)
Asthma control + no increase in therapy – YES n(%)	146 (46.2)	288 (45.6)
Controller–reliever ratio ≥0.5 n(%)	244 (77.2)	448 (70.9)
MPR ≥80% n(%)	48 (15.2)	85 (13.4)
Outcome year ICS dose (µg/d) Median (IQR)	94 (44, 175)	145(72,289)

Numbers in teal indicate P≤0.05

- Asthma Control ± SABA OR ± No Additional Therapy and Severe Exacerbations were similar. The control outcomes showed a consistent trend in favour of EF HFA-BDP.
- The highest numerical difference between EF HFA-BDP and FP patients was seen for Asthma Control + SABA, reinforced by the significantly higher Controller–Reliever ratio recorded for EF HFA-BDP patients.
- ICS dose at prescribed increase, was 320 (320, 320) µg/d and 440 (440, 880) µg/d for EF HFA-BDP and FP respectively. The ratio of mean daily outcome dose to prescribed dose was ~1:3.4 for EF HFA-BDP and ~1:3.0 for FP suggesting similar adherence rates for both treatment groups, reflected by the similar percent of EF HFA-BDP and FP patients with MPR ≥80%.

- To evaluate whether our endpoints were RELEVANT we evaluated their RESPONSIVENESS to effective inter-ventions by comparing them before / after an ICS increase (data pooled for EF HFA-BDP & FP increase patients)

ENDPOINT VALIDATION (all increase patients)	Baseline (948)	Outcome (948)
Asthma control – YES n(%)	435 (45.9)	504 (53.2)
Achieved asthma control + SABA – YES n(%)	277 (29.2)	319 (33.6)
No severe exacerb' ns n (%)	571 (60.2)	679 (71.6)
No asthma hospital' ns n (%)	892 (94.1)	892 (94.1)
No antibiotic use n(%)	767 (80.9	891 (94.0)
Controller–reliever ratio ≥0.5 n(%)	366 (43.3)	692 (73.0)
MPR ≥80% n(%)	29 (3.1)	133 (14.0)

- Asthma control + SABA was the best predictor of guideline-defined endpoints, i.e. low symptoms (using SABA as a proxy), low oral steroid use and low asthma hospitalisations (i.e. low rate of severe exacerbations).

CONCLUSIONS

- EF HFA-BDP achieved similar (or better) outcomes than FP, at significantly lower ICS dose
- The outcome measures used:
  - Showed strong internal consistency
  - Were valid as they proved **responsive** to therapy
- In this US dataset, **Asthma Control + SABA** was a good all-round predictor of guideline-defined asthma control outcomes.

Study funded by Teva Pharmaceuticals Limited

Presented at the European Respiratory Society Annual Congress, Amsterdam, The Netherlands, September 24–28 2011

Appendix 3: Validation literature review

Exacerbations: related literature

- **An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations. Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice**
  Reddel HK, Taylor, DR, Bateman ED et al on behalf of the American Thoracic Society/European Respiratory Society Task Force on Asthma Control and Exacerbations. *Am J Respir Crit Care Med* Vol 180. pp 59–99, 2009

  Asthma Exacerbations
  In clinical practice, exacerbations are identified as events characterized by a change from the patient's previous status. This concept should also be applied in clinical trials.
  1. Severe asthma exacerbations are defined as events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization
  or death from asthma.

- **Asthma outcomes: exacerbations**
  Fuhlbrigge A, Peden D, Apter AJ, et al. *J Allergy Clin Immunol* 2012;129:S34-48

  Defining exacerbations [taken from the Asthma Outcomes Workshop]

  1. Systemic corticosteroids for asthma
  2. Asthma-specific hospitalisations (inpatient admissions)
  3. Asthma-specific Emergency Department / Accident and Emergency (separate UC visits when these can be differentiated)

- **Frequency of non-asthma GP visits predicts asthma exacerbations: an observational study in general practice**
  Hyland ME, Whalley B, Halpin DM, et al. *Prim Care Respir* J 2012

  Background: Being able to identify patients at risk of exacerbations is useful as it enables resources to be targeted at these patients.
  Aims: To test the theoretically-derived prediction that the frequency of non-asthma related visits to the general practitioner (GP) predicts exacerbations.
  Methods: Clinical and demographic data and both self-report and prescription-based adherence data were obtained from 166 patients diagnosed with asthma attending a GP clinic, all of whom were prescribed inhaled corticosteroids (ICS). Asthma exacerbations (treated by the GP or in hospital) and non-asthma visits and symptoms were assessed from notes for the subsequent 5 years.
  Results: Exacerbations correlated with non-asthma visits (0.35), severity as measured by BTS step (0.28), and with prescription-based adherence (0.28). Asthma severity correlated with non-asthma visits (0.35). Receiver operating curves showed that >2 non-asthma visits per year provided 79% sensitivity and 58% specificity for detecting >3 exacerbations over 5 years. Poor adherence predicted outcomes only for patients with high levels of non-asthma

visits (>3) and only for those reporting regular-but-less ICS use but not symptom-directed ICS use.
Conclusions: Non-asthma visits are a good predictor of asthma exacerbations, particular in non-adherent patients. These results are consistent with a mechanism where exacerbations result from a combination of random oscillating specific and non-specific inflammatory processes. It is important to consider the total patient rather than just the lung when managing patients with asthma.

Therapeutic doses: related literature

- **Step-up care improves impairment in uncontrolled asthma: an administrative data study.** (Zeiger RS, Schatz M, Li Q, Zhang F, Purdum AS, Chen W. Am J Manag Care 2010;16:897-906)

  Impairment based on number of SABA canisters[11]

  Impairment was defined as at least 7 short-acting β-agonist (SABA) canisters dispensed in 1 year. In a clinical setting, asthma impairment is defined based on rescue therapy, symptoms, functional limitations, and pulmonary function; however, only rescue therapy use can be obtained in administrative data. We validated the number of SABA canisters dispensed in 1 year as a long-term measure of asthma control because it correlates with patient-reported measures of asthma impairment.[1] The SABA cut point of at least 7 canisters dispensed per year defined impairment because at least 70% more asthma control problems[2] occurred in patients receiving at least 7 vs 6 or fewer canisters dispensed per year.[1]

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- **Development and validation of database indexes of asthma severity and control.** (Firoozi F, Lemiere C, Beauchesne MF, Forget A, Blais L. *Thorax* 2007;62:581-7)

  Defining asthma severity and control

  … the mild asthma category corresponds to ICS doses of 0– 500 mg/day for patients not receiving additional controller therapy and ICS doses of 0–250 mg/day for patients receiving additional controller therapy. Moreover, in order to be classified in this mild category, a patient must not have had a marker of a moderate to severe asthma exacerbation nor have used more than an average

[11] Supports asthma control + SABA composite measure (see above) cut-point of ≤200 µg/d (~<4 canisters/yr)

of three doses of SABA per week during the 12 month period under study. The moderate asthma category corresponds to ICS doses of >500 mg/day for patients not receiving additional controller therapy or doses of >250 mg/day for those receiving additional controller therapy, except for patients with a high use of SABA and moderate to severe asthma exacerbations. Severe asthma is mainly characterised by ICS doses of >1000 mg/day, except for patients with both markers of uncontrolled asthma; for example, patients who are taking more than 10 doses of SABA per week and a marker for a moderate to severe asthma exacerbation.

Patients were considered as controlled if they had no marker for moderate to severe asthma exacerbations and were taking no more than 3 doses of SABA per week for mild asthma [200 mcg x 3 = 600 mcg/7 = 85 mcg/d] and 10 doses of SABA per week for moderate and severe asthma [200 mcg x 10 = 2000 mcg/7 = 285 mcg/d]. In the Quebec cohort the distribution of severity levels was 63%, 23% and 14% for mild, moderate and severe asthma, respectively. This distribution was similar to those of two of the three study populations: 59–66% for mild asthma, around 22% for moderate asthma and 13–19% for severe asthma.

Compliance: related literature

- **Past OPCRD validation work (data on file)**
  The proportion of GPRD patients compliant as defined above using % prescriptions refilled, with an additional filter to identify the % of patients who not only refill their prescriptions, but also take their therapy = 38% of the refill-compliant group. Data source – Optimum Patient Care database (analysis on file). Analysis of the OPC database indicates that among 389 patients who completed a questionnaire– the MARS (Measuring Adherence Rating Scale [see Cohen JL,e t al. Ann Allergy Asthma Immunol. 2009 Oct;103(4):325-31] – assessing compliance with asthma therapy, 62% reported either poor or borderline adherence based on their response to the MARS questions despite ≥70% fulfillment / collection of prescriptions. This results in a "truly compliant population" = those who not only refill their prescriptions, but also take their medication of 38%

Future risk: Related Literature

Resource utilisation

- **Frequency of non-asthma GP visits predicts asthma exacerbations: an observational study in general practice** (Hyland ME, Whalley B, Halpin DM, et al. Prim Care Respir J 2012)

  Background: Being able to identify patients at risk of exacerbations is useful as it enables resources to be targeted at these patients.
  Aims: To test the theoretically-derived prediction that the frequency of non-asthma related visits to the general practitioner (GP) predicts exacerbations.
  Methods: Clinical and demographic data and both self-report and prescription-based adherence data were obtained from 166 patients diagnosed with asthma

attending a GP clinic, all of whom were prescribed inhaled corticosteroids (ICS). Asthma exacerbations (treated by the GP or in hospital) and non-asthma visits and symptoms were assessed from notes for the subsequent 5 years.
Results: Exacerbations correlated with non-asthma visits (0.35), severity as measured by BTS step (0.28), and with prescription-based adherence (0.28). Asthma severity correlated with non-asthma visits (0.35). Receiver operating curves showed that >2 non-asthma visits per year provided 79% sensitivity and 58% specificity for detecting >3 exacerbations over 5 years. Poor adherence predicted outcomes only for patients with high levels of non-asthma visits (>3) and only for those reporting regular-but-less ICS use but not symptom-directed ICS use.
Conclusions: Non-asthma visits are a good predictor of asthma exacerbations, particular in non-adherent patients. These results are consistent with a mechanism where exacerbations result from a combination of random oscillating specific and non-specific inflammatory processes. It is important to consider the total patient rather than just the lung when managing patients with asthma.

- **Improving asthma outcomes in large populations (Schatz M, Zeiger RS. *J Allergy Clin Immunol* 2011;128:273-7)**

Administrative data algorithms for identifying patients at risk of exacerbation
Administrative data. We have developed 2 administrative data algorithms for identifying patients at increased risk of subsequent asthma exacerbations (Table I).[12,13] The first was a 3-level scale developed by using prior emergency department visits and hospitalizations (emergency hospital care) and pharmacy data. This algorithm identified a high-risk group approximately 3 times more likely than other patients to experience a subsequent exacerbation.[12] The second was a 4-level scale based only on pharmacy data that identified a high-risk group more than 6 times more likely to require emergency hospital care than patients in the lowest risk group (Table I).[13] However, comparison of the predictive properties of the 2 schemes suggested that the algorithm including prior emergency hospital care provided a more robust prediction and would thus be recommended if that information was available.[13]

TABLE I. Administrative data algorithms for identifying patients at increased risk of subsequent asthma exacerbations

	Three-level scale[12]	Four-level scale[13]
Predictors	Point allocation	
SABA dispensings in past year	1 for ≥ 14	1 for 5-13 1 for > 13
Oral corticosteroid dispensings in past year	1 for any	1 for > 2
Emergency/hospital care in past year	2	Not used
Intensity scale level	Positive predictive value (%) in testing set by level	
1	6.2 (0 points)	4.0 (0 points)
2	8.1 (1 point)	6.4 (1 point)
3	22.0 (≥2 points)	12.4 (2 points)
4	Not applicable	26.8 (3 points)

TABLE II. Identifying patients for targeted intervention who are at high risk of asthma exacerbations or uncontrolled impairment based on administrative or survey data

Asthma exacerbations
Level 3 in 3-level algorithm (see Table I)
Level 4 in 4-level algorithm (see Table I)
>6 SABA canister dispensings in a 12-mo period
ACT score <16
ATAQ score ≥2
Asthma Impact Survey score >60
AQLQ score ≤4.7
Asthma impairment
>6 SABA canister dispensings in a 12-mo period
ACT score by telephone or survey <20
ATAQ score by survey >0

Cited refs: 12. Schatz M, Nakahiro R, Jones CH, Roth RM, Joshua A, Petitti D. Asthma population management: development and validation of a practical 3-level risk stratification scheme. Am J Manag Care 2004;10:25-32.**13.** Schatz M, Zeiger RS,

Vollmer WM, Mosen D, Apter AJ, Stibolt TB, et al. Development and validation of a medication intensity scale derived from computerized pharmacy data that predicts emergency hospital utilization for persistent asthma. Am J Manag Care 2006;12:478-84.

Rescue medication

- **Improving asthma outcomes in large populations**
  (Schatz M, Zeiger RS. J Allergy Clin Immunol 2011;128:273-7)
  Impairment/risk using SABA scripts
  SABA long-term control scale. The 4-level scale based on canisters of SABAs dispensed over a 12-month period (0-2, 3-6, 7-12, and >12) was validated in a random sample of 2250 Kaiser Permanente patients aged 18 to 56 years with HEDIS-defined persistent asthma and a separate sample of 62,369 members aged 18 to 56 years with persistent or intermittent asthma.[10] A factor analysis performed on information obtained in the former sample by surveys that included the mini-Asthma Quality of Life Questionnaire (AQLQ), the Asthma Therapy Assessment Questionnaire (ATAQ), and the Asthma Outcomes Monitoring Survey showed loading of the 4-level SABA scale on the symptom control factor.10 In addition, impairment, as measured by these validated questionnaires, was linearly related to the 4-level scale (Fig 1).[10] The prospective validity of the scale was tested in the larger sample by assessing the relationship of the scale value during 1 year to emergency hospital care or oral corticosteroid dispensings the following year. A significant linear relationship was also seen between this SABA scale and the subsequent risk of exacerbations (Fig 2).[10]

  Cited ref: 10. Schatz M, Zeiger RS, Vollmer WM, Mosen D, Apter AJ, Stibolt TB, et al. Validation of a b-agonist long term control scale derived from computerized pharmacy data. J Allergy Clin Immunol 2006;117:995-1000.

Appendix 4: Questionnaire used to capture patient reported asthma data

Asthma Questionnaire

Please take a few minutes to complete the whole questionnaire, following the instructions at the head of each section.

In the last week:	0	1	2	3	4	5	6	7	8	9	10+
How many times have you used your reliever inhaler?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Thinking about the last 7 days (please tick one box for each question):	0	1	2	3	4	5	6	7
How many days has asthma interfered with your normal activities (eg sport, school, work/housework)?	☐	☐	☐	☐	☐	☐	☐	☐
How many nights have you been affected/woken by asthma symptoms (including cough)?	☐	☐	☐	☐	☐	☐	☐	☐
How many days have you experienced asthma symptoms?	☐	☐	☐	☐	☐	☐	☐	☐

In the past 4 weeks, did you:	Yes	No	Unsure
Miss any work, school, or normal daily activity because of your asthma?	☐	☐	☐
Wake up at night because of asthma?	☐	☐	☐
Believe that your asthma was well controlled?	☐	☐	☐
In general, do you use an inhaler for quick relief from asthma symptoms?	☐	☐	☐

If yes, in the past 4 weeks, what was the highest number of puffs in 1 day you took of the inhaler?

☐ 0 ☐ 1 to 4 puffs ☐ 5 to 8 puffs ☐ 9 to 12 puffs ☐ More than 12 puffs

In the last 12 months:	0	1	2	3	4	5	6	7	8	9	10+
How many times have you needed a course of steroid tablets for worsening asthma?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
How many days have you had off work/education because of asthma?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

How many times have you been admitted to hospital with breathing or chest problems? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5+

About smoking:

Which best describes you? ☐ Never smoked ☐ Used to smoke, but don't now ☐ Still smoking

	1-5	6-10	11-15	16-20	21-30	31-40	41-50	50+
If you smoke or used to smoke, how many do you/did you smoke per day?	☐	☐	☐	☐	☐	☐	☐	☐
If you smoke, or used to smoke, how many years have you smoked/did you smoke?	☐	☐	☐	☐	☐	☐	☐	☐

	Yes	No
Smoking can make asthma worse - if you still smoke, would you like support from your GP or practice nurse to quit?	☐	☐

About your nose:

Do you have any of these symptoms: itchy, runny, blocked nose or sneezing when you don't have a cold? ☐ No ☐ Occasionally & little bother ☐ Occasionally & quite a bother ☐ Most days but little bother ☐ Most days & a lot of bother

Do any of the following upset your asthma? Tick all that apply. ☐ Colds ☐ Strenuous activity or exercise ☐ Allergies eg cats, dogs, pollen ☐ Cigarette smoke

Please complete other side

Appendix 5: OPCRD data dictionary

1. Patient

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

Field Name	*Content*
Patient_ID	Anonymised patient identifier
Practice_ID	Unique practice identifier.
Year_Of_Birth	Patient year of birth in format YYYY
Gender	Patient gender
Status	Patient registration status - (R) – Registered, (L) – Left, (D) - Death
Joined_Date	Date joined practice or date first registered on database
Leaving_Date	Date left practice or date first registered on database
Leaving_Reason	Reason for leaving practice
Post_Code	"Out" part of patient postcode and first character of "in" part of patient post code

2. Clinical

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

Field Name	*Content*
Patient_ID	Anonymised patient identifier
Event_Date	Date of event
Read_Code	Five byte read code for event including terminal code if available
Read_Term	Rubric associated with read_code
Numeric_1	First numeric value if stored
Numeric_2	Second numeric value if stored
Text	First 50 characters of any text associated with entry

3. Referral

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

Field Name	*Content*
Patient_ID	Anonymised patient identifier
Event_Date	Date of event in format dd/mm/yyyy

Read_Code	Five byte read code for event including terminal code if available
Read_Term	Rubric associated with read_code
Referral_Type	Referral type e.g. Outpatient
Referral_To	Organisation referred to
Specialism	Referral by e.g. GP referral
Attendance_Type	Attendance type e.g. First visit, follow up

4. Therapy

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

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

5. Practice

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

Field Name	*Content*
PracticeID	Unique OPC practice id
Practice_NHS	Unique NHS practice identifier.
Practice_Name	Name of practice
Practice_Address1	Address line 1
Practice_Address2	Address line 2
Practice_Address3	Address line 3
Practice_Address4	Address line 4
Practice_Postcode	Post Code
Practice_list_size	Total practice list size
Last_Extract_Date	Date when practice last did an extract

6. Asthma Questionnaire Data Collection

The **Asthma Questionnaire Data Collection** file contains the data collected from the questionnaires received from patients participating in the OPC Asthma Review Service. The file provides the original response as well as calculated values derived from the patient responses to the questions. Questions currently being surveyed are the following:

Questions	***Answer Options***
In the last week, how many times have you used your reliever inhaler (usually blue).	0–9; ≥10
In the last 7 days, how many days has asthma interfered with your normal activities?	0–7
In the last 7 days, how many nights have you been affected/woken by asthma symptoms (including cough)?	0–7
In the last 7 days, how many days have you experienced asthma symptoms?	0–7
In the last 4 weeks, did you miss any work, school or normal daily activity because of your asthma?	Yes; No; Unsure
In the last 4 weeks, did you wake up at night because of asthma?	Yes; No; Unsure
In the last 4 weeks, did you believe that your asthma was well controlled?	Yes; No; Unsure
In the last 4 weeks, in general, do you use an inhaler for quick relief from asthma symptoms?	Yes; No; Unsure
If yes, in the past 4 weeks, what was the highest number of puffs in 1 day you took of the inhaler?	0 / 1 to 4 puffs; 5 to 8 puffs; 9 to 12 puffs; More than 12 puffs
In the last 12 months, how many times have you needed a course of steroid tablets for worsening asthma.	0–9; ≥10
In the last 12 months, how many days have you had off work/education because of asthma.	0–9; ≥10
In the last 12 months, how many have you been admitted to hospital with breathing or chest problems?	0–9; ≥10
In the last 12 months, how many time have you been treated in accident and emergency or anywhere other than your GP surgery for your asthma?	0–9; ≥10
About smoking, which best describes you?	1 = Never smoked, 2 = Current Smoker, 3 = Ex-smoker
If you smoke or used to smoke, how many cigarettes do you/did you smoke per day?	1-5; 6-10; 11-15; 16-20; 21-30; 31-40; 41-50; >50
If you smoke, or used to smoke, how many years have you smoked/did you smoke?	1-5; 6-10; 11-15; 16-20; 21-30; 31-40; 41-50; >50

Smoking can make asthma worse - if you still smoke, would you like support from your GP or practice nurse to quit?	Yes / No
Do you have any of these symptoms: itchy, runny, blocked nose or sneezing when you don't have a cold?'	No / Occasionally & Little Bother / Occasionally & Quite a Bother / Most days & Little Bother / Most Days & a lot of bother
Do any of the following upset your asthma?	Colds / Strenuous Activity & Exercise / Allergies eg cats, dogs, pollen / Cigarette smoke
Thinking about how often you take your regular Asthma treatment during the day:	1 = I always take it exactly at the time prescribed. 2 = I occasionally miss the odd dose. 3 = I often miss or forget to take doses. 4 = I take all once a day- it's easier. 5 = I never take it.
I think my inhaler technique is very poor / I think my inhaler technique is excellent.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I do not need to take my inhaler(s) for my asthma to be well controlled / I need to take my inhalers(s) regularly for my asthma to be well controlled.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I find my inhaler(s) easy to use / I find my inhaler(s) difficult to use.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
Taking regular asthma medication does not worry me / Taking regular asthma medication worries me.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I prefer to take my asthma medications in a twice daily dose / I prefer to take my asthma medications in a once a day dose.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I use it regularly / I use it only when I feel breathless.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I never avoid using it if I can / I always avoid using it if I can.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I never forget to take it / I always forget to take it.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I never decide to miss a dose / I always decide to miss a dose.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
I never choose to take it once a day / I always choose to take it once a day.	An answer from 1 to 6 will indicate which statement best describes how they use their inhaler.
When using preventer inhaler, do you feel a sensation at the back of the throat?	Yes / No
When using preventer inhaler, do you sometimes feel a need to cough?	Yes / No
When using preventer inhaler, do you feel your medication is deposited at the back of your throat?	Yes / No

Experience any side effects for the preventer inhaler?	Yes / No
Perceived Side Effects: Continual sore throat?	Yes / No
Perceived Side Effects: Hoarse voice?	Yes / No
Perceived Side Effects: Oral Thrush?	Yes / No
Perceived Side Effects: Abnormal Weight Gain?	Yes / No
Perceived Side Effects: Bruising?	Yes / No
Perceived Side Effects: Cough?	Yes / No
Have you had your inhaler technique checked in the last 12 months?	Yes / No
Have you seen a specialist respiratory doctor or nurse outside the practice?	Yes / No
Do you have a peak flow meter?	Yes / No
If you have a peak flow meter, please tell us your reading today?	Value
In the future, would you be willing to participate in further research?	Yes / No
Do you have a preventer inhaler?	Yes / No

7. COPD Questionnaire Data Collection

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

Question	***Answer Options***
I never cough / I cough all the time.	An answer from 1 to 6 will indicate which statement best describes the impact COPD is having on their wellbeing and daily life.
I have no phlegm (mucus) on my chest at all / My chest is completely full of mucus.	An answer from 1 to 6 will indicate which statement best describes the impact COPD is having on their wellbeing and daily life.
My chest does not feel tight at all / My chest feels very tight.	An answer from 1 to 6 will indicate which statement best describes the impact COPD is having on their wellbeing and daily life.
When I walk up a hill or one flight of stairs I am not breathless / When I walk up a hill or one flight of stairs I am very breathless.	An answer from 1 to 6 will indicate which statement best describes the impact COPD is having on their wellbeing and daily life.
I am not limited doing any activities at home / I am very limited doing activities at home.	An answer from 1 to 6 will indicate which statement best describes the impact COPD is having on their wellbeing and daily life.
I am confident leaving my home despite my lung condition / I am not at all confident leaving my home because of my lung condition.	An answer from 1 to 6 will indicate which statement best describes the impact COPD is having on their wellbeing and daily life.
I sleep soundly / I don't sleep soundly because of my lung	An answer from 1 to 6 will indicate which statement best describes the impact COPD

condition.	is having on their wellbeing and daily life.
I have lots of energy / I have no energy at all.	An answer from 1 to 6 will indicate which statement best describes the impact COPD is having on their wellbeing and daily life.
I need to take my inhaler(s) regularly.	Strongly Disagree / Disagree / Not sure / Agree / Strongly Agree
I find inhaler(s) difficult to use.	Strongly Disagree / Disagree / Not sure / Agree / Strongly Agree
I worry about the side effects of my COPD inhaler(s).	Strongly Disagree / Disagree / Not sure / Agree / Strongly Agree
I have enough information about my inhaler(s).	Strongly Disagree / Disagree / Not sure / Agree / Strongly Agree
I would prefer to take my regular COPD medications in a once-a-day dose.	Strongly Disagree / Disagree / Not sure / Agree / Strongly Agree
Thinking about how often you take your regular COPD treatment during the day:	1 = I always take it exactly at the time prescribed. 2 = I occasionally miss the odd dose. 3 = I often miss or forget to take doses. 4 = I take all once a day- it's easier. 5 = I never take it.
Which statement best describes how you take your regular COPD treatment.	1 = I take it every day. 2 = I take some days but others I do not. 3 = I used to take but now I do not. 4 = I take only when I have symptoms. 5 = I never take it.
Have you seen a specialist respiratory doctor or nurse outside the practice?	Yes/No
Thinking about breathlessness, which statement best describes you?	1 = Not troubled by breathlessness. 2 = Short of breath when hurrying or walking up a slight hill. 3 = Slower in walking than other of the same on the level because of breathlessness, or have to stop for breath when walking at your own pace. 4 = Stopping for breath after about 100m or after a few minutes on the level. 5 = Too breathless to leave the house, or breathless when dressing / undressing.
Which best describes you?	1 = Never smoked, 2 = Current Smoker, 3 = Ex-smoker
How many cigarettes do/did you smoke per day?	1-5; 6-10; 11-15; 16-20; 21-30; 31-40; 41-50; >50
How many years have you smoked/did you smoke?	1-5; 6-10; 11-15; 16-20; 21-30; 31-40; 41-50; >50
In the past year, have you had your Inhaler technique checked?	Yes/No
In the past year, how many times have you been admitted to hospital with breathing problems?	0, 1, 2, 3, 4, 5 or more
In the past year, how many times have you had a worsening of your chest symptoms requiring a course of steroid tablets and/or antibiotics?	0, 1, 2, 3, 4, 5 or more
Do you have any of these symptoms: itchy, runny, blocked nose or sneezing when you	Yes/No

don't have a cold?	
Thinking about exercise, how much time do you spend doing exercise/activity (eg walking) each day?	None / 15mins / 30mins / 45mins / 1 hr / 2 hrs / 3 hrs or more
In the future, would you be willing to participate in further questionnaire based research?	Yes/No
Do you have home oxygen therapy (either cylinders, liquid oxygen or a concentrator?)	Yes/No

Appendix 6: Interaction between smoking status and SABA usage (RiRL – unpublished data)

Current smokers in both the ICS initiation and step-up cohorts from a (as yet unpublished) study carried out by Research in Real Life, using a pooled CPRD & OPCRD dataset, indicate consistently higher SABA use among smokers. Given the routine higher SABA usage seen among smokers, the control definition that factors in a maximum threshold for SABA usage associated with asthma control will be evaluated (as discussed in the preceding study protocol) for patient subgroups split by smoking status.

Initiation Patients		**Smoking status**			
		Non smoker	Current Smoker	Ex-Smoker	Total
Outcome SABA Daily Dosage	1-100	9428 (24.5)	3913 (15.3)	5752 (25.2)	19093 (22)
	101-200	10741 (27.9)	6193 (24.2)	6134 (26.9)	23068 (26.5)
	201-400	10464 (27.2)	7380 (28.8)	6131 (26.9)	23975 (27.6)
	401-800	5824 (15.1)	5263 (20.5)	3582 (15.7)	14669 (16.9)
	801+	2081 (5.4)	2884 (11.3)	1213 (5.3)	6178 (7.1)
Total		38538 (100)	25633 (100)	22812 (100)	86983 (100)

Step-up Patients		**Smoking status**			Total
		Non smoker	Current Smoker	Ex-Smoker	
Outcome SABA Daily Dosage	1-100	3682 (17.2)	953 (8.9)	1654 (16.2)	6289 (14.8)
	101-200	3930 (18.4)	1396 (13.0)	1806 (17.7)	7132 (16.8)
	201-400	5820 (27.2)	2495 (23.2)	2651 (26.0)	10966 (25.9)
	401-800	5016 (23.4)	3034 (28.2)	2549 (25.0)	10599 (25.0)
	801+	2950 (13.8)	2873 (26.7)	1544 (15.1)	7367 (17.4)
Total		21398 (100)	10751 (100)	10204 (100)	42353 (100)