

OPC Global
Study protocol

Study protocol

Hidden Severe Asthma in Primary Care versus ISAR Cohort

Describe the extent of patients with severe asthma who are treated solely in a primary care setting and compare their demographic and clinical characteristics to ISAR.

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21/02/2019

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Marketing authorisation number	Not applicable
Study aims and objectives	<p>Aim: To identify, within asthma managed population, patients that have severe asthma but are “hidden” from specialist care using a large, real-life population-based cohort of patients in the UK.</p> <p>To compare the demographic and clinical characteristics of “hidden” patients with severe asthma identified in primary care to those managed in specialist care.</p> <p>Primary objective: To construct criteria for identifying severe asthma in primary-care Electronic Medical Record (EMR) databases based on their treatment and measures of control.</p> <p>To compare the characteristics of “hidden” patients with severe asthma in primary care to patients managed in specialist care, within the International Severe Asthma Registry (ISAR).</p> <p>Secondary objective: To describe the demographic and clinical profile of patients with severe asthma managed exclusively in primary care and are <i>hidden</i> from specialist care.</p> <p>To describe the demographic and clinical profile of patients treated at low dose ICS/LABA and experiencing exacerbations. These patients may be <i>unrecognised</i> as potentially severe asthma patients.</p> <p>To create a criteria-template for identifying these patients with severe asthma in other countries</p>
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1.0 Background

Severe Asthma prevalence

Expert opinion indicates that severe asthma prevalence is between 5 and 10%;¹ however more recent studies using observation data have been undertaken to measure the prevalence of severe asthma in primary care populations.

A Swedish study investigated the phenotype of 2,006 subjects and 36% had 1 sign indicating severe asthma whilst 13% had two signs.² A Danish study investigated 61,583 18-44 year olds with ≥ 2 respiratory prescriptions found that patients with severe asthma represented 8.1% of the asthma population.¹ A study of 18,724 patients with asthma over 18 years of age found those with severe asthma represented 4.2% of the asthma population.³ Whilst a Dutch study which differentiated between patients with severe asthma and those who were difficult to control due to poor medication compliance or poor inhaler technique found patients with severe asthma represented 3.6% of the population.⁴

Thus the prevalence of severe asthma has been reported as between 3.6-36% of patients with asthma. This range in prevalence rates is due to differing definitions of severe asthma, various study methodologies and patient population inclusion.¹⁻⁴

Specialist care for patients with severe asthma

Guidelines recommend early and appropriate referral to specialist centres for patients with severe asthma to a) assure diagnostic accuracy, b) determine specific asthma phenotypes c) identify and control comorbidities, poor adherence, and patient's inhaler techniques. The prevalence studies that detailed the number of patients with severe asthma that received specialist contact reported between 20 and 34% of patients with severe asthma had contact with a respiratory specialist in the 1 year period of observation.^{1,3}

Patients with severe asthma that aren't referred to respiratory specialists remain hidden in primary care and can be exposed to frequent courses of oral corticosteroids^{3,5} which place them at risk of multiple side effects from oral corticosteroid exposure.^{1,6} Possible reasons for lack of referral include:

- **Clinical inertia:** Patients and physicians are complacent in a management strategy which has been shown to be effective, affordable and at least superficially safe i.e. inhaled corticosteroids (ICS) plus additional inhalers and repeated short courses of oral corticosteroids (OCS) in acute exacerbations.
- **Primary care disease:** Asthma is considered to be a non-critical disease that should be managed almost exclusively in primary care. Payors often discourage specialist referrals

and referring patients to an asthma specialist might be considered as a failure by primary care physicians.

- **Lack of awareness:** of appropriate referral to improve patient outcomes, access therapeutic options available in specialist centres, and reduce side effects that result from frequent use of OCS.
- **Patients expectations:** are that asthma to cause symptoms and exacerbations, and may trade off using maintenance treatments against significant symptoms.⁷ As a result poor control of asthma is rife and this is reflected in frequent exacerbations, emergency care visits in primary and secondary care and high symptom burden.

Patients with severe asthma have much to gain from referral to severe asthma services including a comprehensive review of diagnosis, triggers and treatable traits. Optimising medication in terms of guideline based use of inhaled treatments, appropriate use of oral steroids with self-management education and written action plans, and correct device choice and technique of use. Additionally, use of specialist medications such as long acting muscarinic drugs, macrolides and new biologics may have real benefits to carefully selected patients.⁸

There is a need to improve the identification of undiagnosed patients with severe asthma within primary care who would benefit from an appropriate referral, assessment and personalised therapy. This could improve quality of life, reduce morbidity and/or mortality associated with severe asthma.²

By convening primary and secondary care asthma experts; this study will construct criteria to identify the extent of “hidden” and unrecognised patients with severe asthma within managed asthma populations in primary care setting in the UK. This definition will be used as a basis to interrogate EMRs in other countries to better understand the global dispersion of hidden severe asthma in primary care. Further, this will enable development of algorithms and/or clinical pathways to identify hidden severe asthma in primary care EMRs promoting earlier referral to specialists in the future. This study will also compare the demographic and clinical profile of patients with “hidden” or unrecognised severe asthma identified in primary care to those managed in specialist care.

Study aims

- To identify, within asthma managed population, patients that have severe asthma but are “hidden” from specialist care using a large, real-life population-based cohort of patients in the UK.
- To compare the demographic and clinical characteristics of “hidden” patients with severe asthma identified in primary care to those managed in specialist care.

Study objectives

Primary objectives:

- To construct criteria for identifying severe asthma in primary-care EMR databases based on their treatment and measures of control.
- To compare the characteristics of “hidden” patients with severe asthma in primary care to those managed in specialist care (ISAR).

Secondary objectives:

- To describe the demographic and clinical profile of patients with severe asthma managed exclusively in primary care and are *hidden* from specialist care.
- To describe the demographic and clinical profile of patients treated at low dose ICS/LABA and experiencing exacerbations. These patients may be *unrecognised* as potentially severe asthma patients.
- To create a criteria-template for identifying these patients with severe asthma in other countries.

2.0 Study design

Study design

This study is a descriptive historical cohort study to identify patients with severe asthma in primary care setting in UK. This analysis will undertake to identify two groups of patients with severe asthma.

The first group to be identified are patients that are treated according to the GINA definition and remain hidden from specialist referral. GINA defines severe asthma as *“that requires GINA Step 4 or 5 treatment, e.g. high-dose ICS/LABA, to prevent it from becoming ‘uncontrolled’, or asthma that remains ‘uncontrolled’ despite this treatment.”*

Following this definition patients will be classified according to a) the level of treatment, and b) whether they are controlled.^{9,10} Control will be measured using a) diagnosis of exacerbations, b) excessive SABA use and, c) RCP questions recorded as part of an asthma review.

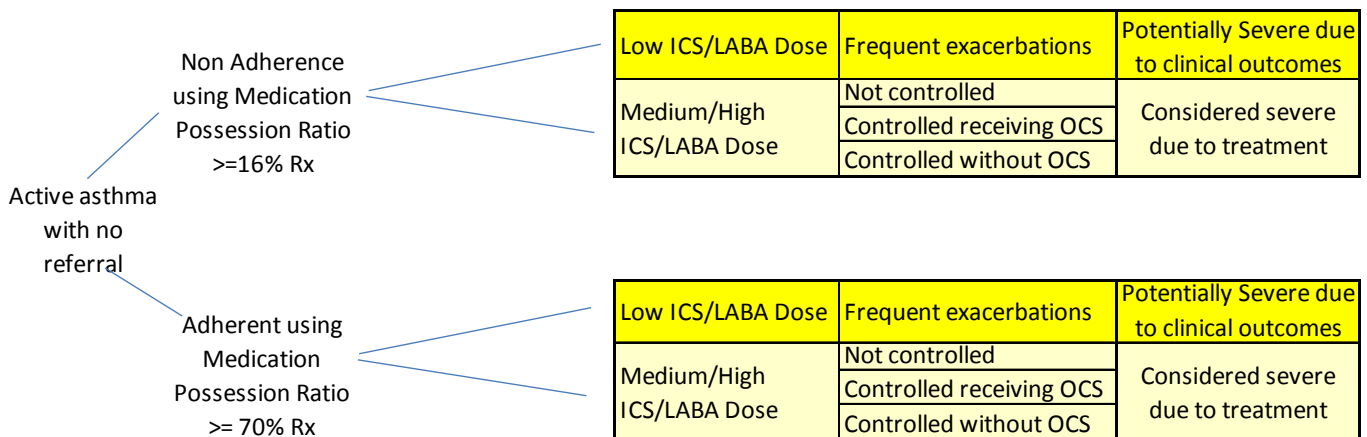
Patients will be classified as hidden if they don't have a record of an asthma related outpatient attendance, an asthma related hospital admission. Patients will remain hidden if they have non asthma related hospital attendances or an Emergency Room (ER) attendance.

The second group to be identified are patients that are receiving low dose ICS/LABA, GINA step 3, who are not controlled and are potentially severe based upon their clinical outcomes (Figure 1). These are potentially *unrecognised* patients with features of severe asthma who are possibly being treated sub-optimally.

This study will compare the characteristics of the hidden patients (GINA step 4 uncontrolled and GINA step 5) to patients registered with the International Severe Asthma Registry. The second group (treated at GINA step 3) characteristics will be described.

Definitions will be refined by OPC and a Steering Committee composed of primary and secondary care asthma experts.

Figure 1: Patient Flow Selection



Study Population

2.2.1 Optimum Patient Care Research Database

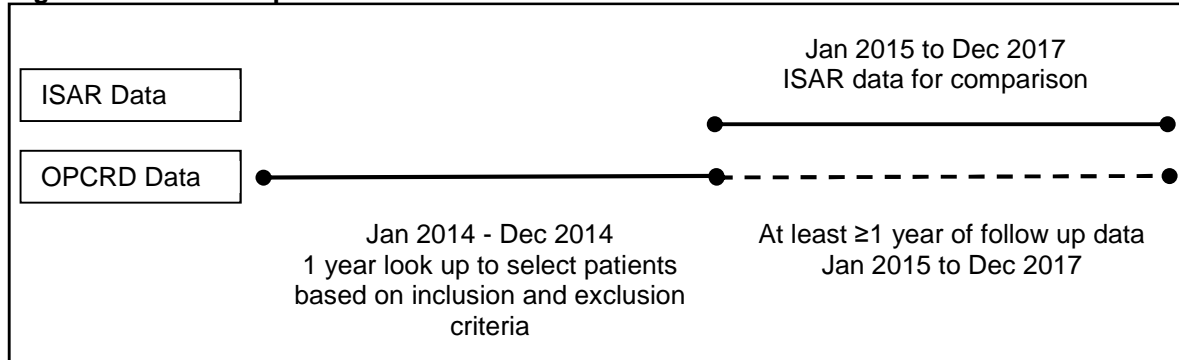
Patients with Severe asthma will be extracted from the OPCR database using the following criteria.

Inclusion criteria
<ul style="list-style-type: none"> • Age ≥ 16 years old • Patients with ≥ 1 year of data after the lookup period (including patients who died during this time) (Figure 2) • Patients with: <ul style="list-style-type: none"> ○ An active diagnostic Read code for asthma (appendix 11.1) qualifying inclusion in the asthma QOF registry, ○ No subsequent recorded asthma resolved Read code after the last asthma diagnosis, ○ Receiving ≥ 1 GINA step 4/5 asthma medications (appendix 11.2) in the one year lookup period.

Exclusion criteria

- Patients with physician confirmed diagnosis of other respiratory conditions (appendix 11.3)
- Patients with a primary care record of an asthma outpatient attendance or an asthma admission (appendix 11.4)

Figure 2: Data lookup and extraction timelines



Oral corticosteroids scripts will be classified as probable acute or probable chronic using the algorithm specified below (figure 3).

An example of a flow chart to ascertain a primary care EMR appropriate definition after iterative results and discussions with the steering committee is shown in Figure 4.

2.2.2 International Severe Asthma Registry

Patients with severe asthma treated at GINA step 4 and GINA step 5 specified above (2.2.1) will be compared to the UK International Severe Asthma Registry (ISAR). The inclusion criteria for these patients are shown below.

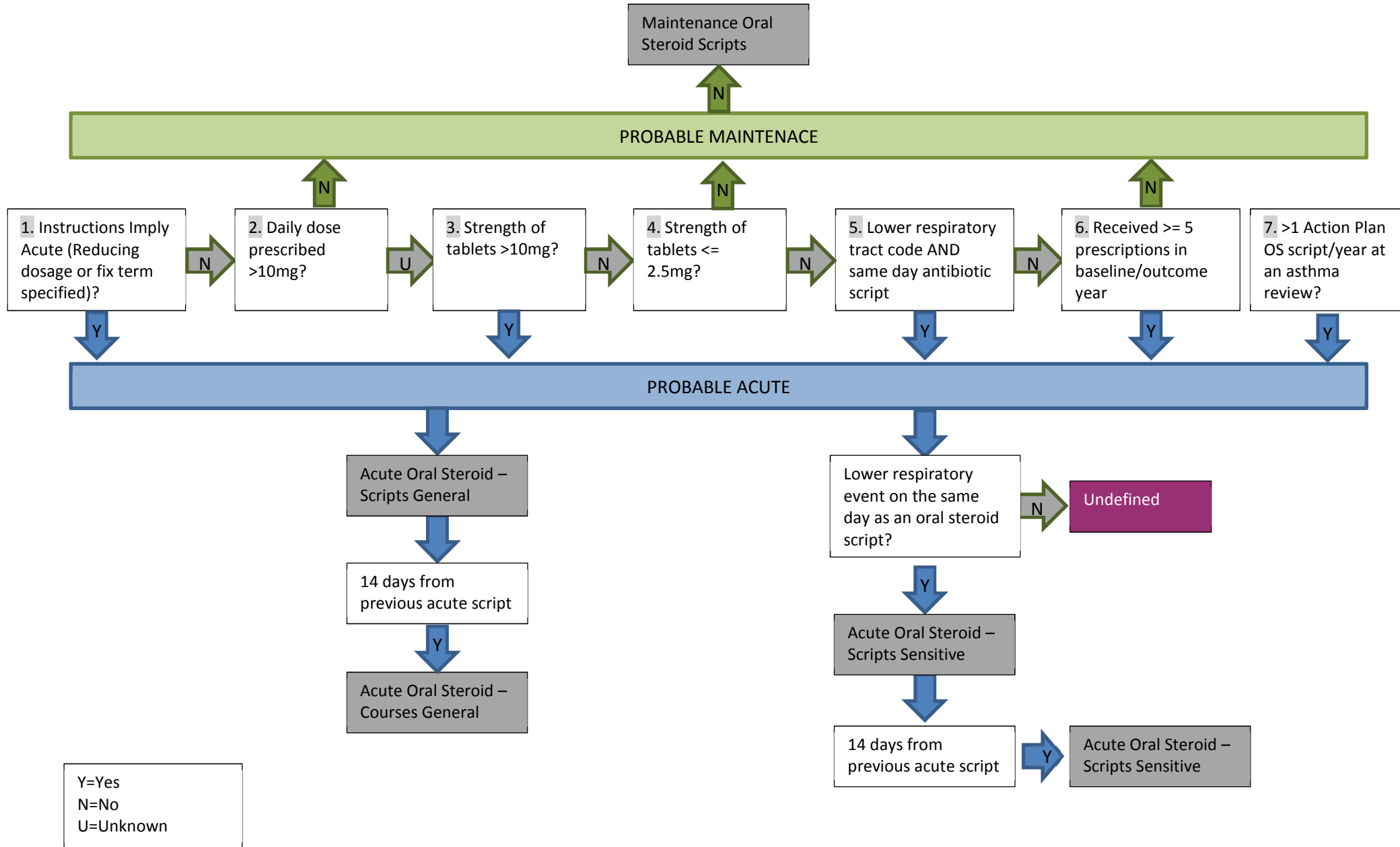
Inclusion criteria

- Age ≥ 18 years old
 - Patient on GINA Step 5 treatment
- OR
- Patient on GINA Step 4 treatment with
 - Severe asthma symptoms
 - Frequent exacerbations requiring systemic corticosteroids

Exclusion criteria

- Lack of consent to share de-identified medical information

Figure 3: Algorithm to define an acute or maintenance prescription for oral steroids



Data source

Optimum Patient Care Research Database (OPCRD) UK: a quality-controlled research database that complements routinely-recorded disease coding and prescribing information with patient-reported outcomes. It is developed, maintained, and owned by Optimum Patient Care (OPC), a social enterprise company that aims to improve patient outcomes through medical research and services. It currently comprises anonymous, longitudinal data for over 5.7 million patients from over 700 UK general practices. This database has received a favourable opinion from the Health Research Authority for clinical research use (REC reference: 15/EM/0150).

International Severe Asthma Registry (ISAR): The ISAR registry is a multi-country, multicentre, observational epidemiologic data repository, with retrospective and prospective data of patients with severe asthma. The key feature of the registry is its standardised data fields irrespective of data source. ISAR includes a combination of existing and new severe asthma registries, where primary data is collected via eCRFs on a web-based platform. Person-level data from the UK as defined by the inclusion criteria in section 2.2, will be used to provide a comparison to the population hidden in primary care.

ISAR and OPCRD have governance provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG).

3.0 Study variables and study outcomes

The following list of demographic and clinical variables will be used to describe patients with severe asthma from primary care centres and to compare their characteristics with those identified in ISAR.

Demographic variables

Variable Name ¹	Description
Age	Age in years at the date of first asthma review with lung function data
Gender	Female or Male
Height	Patients height
Ethnicity	Caucasian, Black, South East Asian, North East Asian
Body Mass Index (BMI)	Defined as the ratio of weight (kg) to squared height (m ²). Categorised as: underweight (< 18.5 kg/m ²), normal weight (≥ 18.5 kg/m ² and < 25 kg/m ²), overweight (≥ 25 kg/m ² and < 30 kg/m ²), obese (≥ 30 kg/m ²)
Smoking Status	Categorised as non-smoker, current smoker or ex-smoker
Pack years	Defined as the number of cigarettes smoked per day divided by 20 and multiplied by the number of years smoked
Mortality	Patients who have died due to an asthma related condition (defined as a patient being transferred out of the practice with a respiratory diagnosis)

¹ All variables are measured at baseline; which will refer to the first patient visit where data is collected for ISAR

Clinical Variables

Variable Name ¹	Description
Number of exacerbations	Number of asthma exacerbations requiring oral corticosteroids during the study period or diagnosis of pneumonia
Exacerbation years	Number of years with at ≥1 exacerbation
Primary care physician visits	Number of asthma-related visits to primary care physician during the study period
Invasive ventilations	Number of episodes of invasive ventilation ever (appendix 11.11)
Hospital/inpatient admissions	Number of inpatient admissions for respiratory condition recorded in primary care record
A&E attendances	Number of emergency attendances for respiratory recorded in primary care record
Asthma Control	<p>OPCRD Patients</p> <ol style="list-style-type: none"> Royal College of Physicians Asthma 3-Questions¹¹ EMR definition of asthma control¹² <p>a) Risk Domain Asthma Control (RDAC): Uncontrolled if any of the following during the 12-month assessment period:</p> <ul style="list-style-type: none"> Primary care exacerbation Read Code; acute use of OCS with evidence of respiratory review; antibiotics prescribed with evidence of respiratory review <p>b) Overall Asthma Control (OAC): Used an average daily SABA dose of >200 mcg salbutamol or >500 mcg terbutaline (corresponding to >3.65 SABA canisters in 12 months)</p> <p>ISAR patients</p> <p>Categorised as controlled, partly controlled or uncontrolled according to the GINA Asthma Control Criteria/Asthma Control Questionnaire (ACQ)/Asthma Control Test (ACT)</p>
Comorbidities (ever/never)	Nasal polyps, Chronic rhinosinusitis, Eczema, Allergic Rhinitis, Diabetes, CKD, Hypertension, GERD, Heart failure, Psychiatric conditions (Anxiety/Depression), Pneumonia (one broad, one narrow with concurrent XRay or hospital appointment), Osteoporosis, Glaucoma/Cataract, IHD (appendix 11.12)
Blood eosinophil count	Count of blood eosinophils, measured in cells per litre (10 ⁹ /L). Categorised as ≤0.15, >0.15 - ≤0.3, >0.3 - ≤0.45 >0.45
Predicted FEV ₁ (Taken at the same time as an asthma review)	Predicted value of Forced Expiratory Volume in the first second of expiration Where available this will be standardised according to ethnicity, age, gender, and height
Peak Expiratory Flow (PEF) (Taken at the same time as an asthma review)	Peak expiratory flow (L/min) recorded using read code
FEV ₁ /FVC Ratio (Taken at the same time as an asthma review)	Measured FEV ₁ as a ratio of measured FVC
Fractional exhaled nitric oxide (FeNO) test	Measurements of fractional nitric oxide concentration in exhaled breath, measured in parts per billion (ppb) at a flow rate of 50mL/ s. low (<25ppb), intermediate (25-50) high (>50ppb)
Medication Possession Ratio (MPR)	Good adherence to treatment defined as a Medication Possession Ratio ¹³ (MPR) ≥70%, measure based on ICS prescription refills

(Surrogate marker for adherence)	
Oral corticosteroid Rxs	Number of prescriptions of OCS Dose/Length of Course of OCS Cumulative annual dose
Acute oral corticosteroids	Number of acute courses of OCS ≥2 bursts of systemic OCS, 30 mg or higher for 5 – 14 days
ICS use	Number of prescriptions for inhaled corticosteroids and daily dose
Antibiotics prescriptions	Number of antibiotics prescriptions for respiratory infection
Respiratory treatments	LABA, LAMA ICS/LABA, ICS/LABA/LTRA, Antibiotics, Theophyllines Monoclonal antibodies (if recorded) Allergic rhinitis medications Ratio of ICS Rx : Total respiratory Rx

Mapping ISAR level of control categorisation to OPCRD measures of control

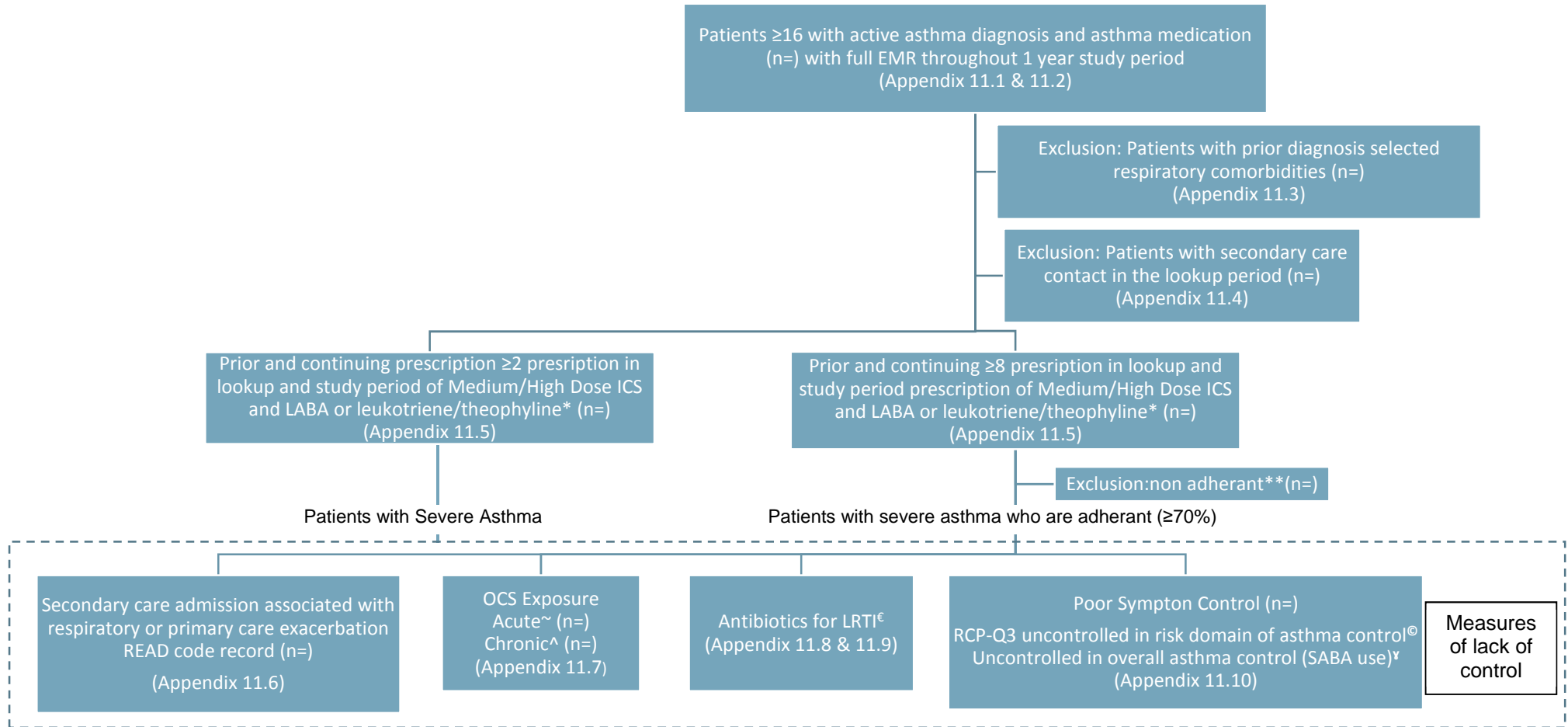
ISAR	Combined definition	OPCRD
Poorly controlled (ACT or ACQ)	Not Controlled	SABA use >3.65 canisters x in 12 months ¹² <u>or</u> Primary Care exacerbation coding <u>or</u> 'yes' to RCP3 questions relating to night time waking or activity limitations ¹⁴
Not Well Controlled (ACT or ACQ)		
Well Controlled (ACT or ACQ)	Controlled	SABA use <3.65 canisters in 12 months ¹² <u>or</u> no primary care exacerbation coding <u>or</u> 'no' to RCP3 questions night time waking or activity limitations ¹⁴

Study Outcomes

The study will describe the, the patients with severe asthma and adherent patients with severe asthma populations in the 1 year baseline period and the 3 year study period. Study outcomes will be reported as mean and categorical numbers (%) for those patients in the outcome period.

	ISAR	OPCRD
Age, categorical 16-17 18-34 35-54 55-79 80+	16-17 Not available n (%) ≥18	16-17 - n (%) n (%) ≥18
Sex Female Male	n (%)	n (%)
Smoking status Current smokers Ex-smokers Non-smokers	n (%)	n (%)
No. of exacerbations 0, 1, ≥2	n (%)	n (%)
No. of years with at least one exacerbation	n (%)	n (%)
Asthma control Poorly controlled Not well controlled Well controlled	n (%) (measured using ACT or ACQ)	n (%) (measured using primary care coding of exacerbation, RCP3 questionnaire, and risk domain asthma control and/or, SABA use)
Mortality Rates	Not available	n (%)
Blood eosinophil count <0.15 >0.15 - ≤0.30 >0.30 - ≤0.45 >0.45	n (%)	n (%)
Adherence (MPR) >70%	n (%)	n (%)
Asthma medication LABA, LAMA ICS/LABA, ICS/LABA/LTRA, Antibiotics, Theophyllines Monoclonal antibodies (if recorded)	n (%)	n (%)
Comorbidities Allergic rhinitis Eczema Nasal Polyps Chronic rhinosinusitis Hypertension GERD HF Anxiety/Depression Osteoporosis Glaucoma/Cataract IHD	n (%) available ≥2017 available ≥2017 available ≥2017 available ≥2017 available ≥2017 available ≥2017 available ≥2017	n (%) available ≥2017 available ≥2017 available ≥2017 available ≥2017 available ≥2017 available ≥2017 available ≥2017

Figure 4: A potential process of identifying hidden severe asthma in primary care (to be further developed by the steering committee)



* **Medium dose:** >250-500µg FP equivalent per day, **High dose:** >500µg FP equivalent per day

** **Non-adherence:** ICS Medication Script Issued <70%

~ **Acute OCS:** ≥2 bursts of systemic CS, 30 mg or higher for 5 – 14 days

^ **Chronic OCS:** 5 mg or more of prednisolone for at least 3 months **OR** Approximately 20 mg/d of prednisolone for at least 3 successive months **OR** 10 to 30 mg/d for 4 prescriptions per day.

€ **Antibiotics for respiratory infection:** Antibiotic prescription related to a respiratory infection diagnosis

© **Risk Domain Asthma Control (RDAC):** Uncontrolled if either an Asthma-related hospital admission, ED or outpatient department attendance, Acute use of OCS with evidence of respiratory review, Antibiotics prescribed with evidence of respiratory review during the 12-month assessment period

¥ **Overall Asthma Control (OAC):** Uncontrolled if uncontrolled RDAC or used an average daily SABA dose of >200 mcg salbutamol or >500 mcg terbutaline (corresponding to >3.65 SABA prescriptions in 12 months)

4.0 Statistical analysis

- Report the number of hidden patients with severe asthma
- Descriptive statistics on demographic and clinical characteristics will be provided for continuous and categorical variables accordingly:
 - For variables measured on the interval or ratio scale, summary statistics produced will be:
 - Sample size (n)
 - Percentage non missing
 - Mean
 - Variance/standard deviation
 - Range (minimum- maximum)
 - Median
 - Inter-quartile range (25th and 75th percentile)
 - For categorical variable the summary statistics will include:
 - Sample size (n)
 - Range (if applicable)
 - Count and percentage by category (distribution)
- Standardised mean differences will be used to compute the imbalance in demographic and clinical characteristics between patients with severe asthma identified in the primary care centres versus ISAR.

Stata version 14 (College Station, TX, USA) or SAS version 9.4/9.5 (Cary, NC, USA) will be used to conduct all statistical analyses and data manipulations.

Significance testing

Characteristics of patients with severe asthma in primary care centres and ISAR will be compared via contingency tables and group difference will be tested for statistical significance via Chi-square tests for comparison of categorical counts. Student t-test or one-way analysis of variance (ANOVA) will be applied to test for statistical significance for comparison of means. Statistical significance will be defined as $p < 0.05$.

Group characterisation

Univariate analysis

Univariate distributions for patient characteristics (age, gender, BMI, smoking status (including pack years), and mortality) and clinical characteristics listed in section 3.2 will be described for patients with “hidden” severe asthma identified in primary care centres and patients within the International Severe UK Asthma Registry.

5.0 Regulatory and ethical compliance

This study was designed and will be implemented and reported in accordance with the criteria of the “European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study” and follows the ENCePP Code of Conduct (EMA 2014). Once a final version of the protocol has been agreed and reviewed by the advisory group, this study will be registered with www.encepp.eu. Governance will be provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee.¹⁵

All sites will enter into a regulatory agreement in compliance with the specific data transfer laws and legislation pertaining to each country and its relevant ethical boards and organisations.

Further, all data extracted to be transferred from sites will be hashed and will enter the research database in the form of anonymised patient IDs. The data will be retrieved by OPC data analysts and utilised as an anonymised dataset to perform the analysis according to protocol.

The study will be performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices.

6.0 Data dissemination

Distinct results from this study will be submitted in abstract form for REG 2020, ATS 2020, and ERS 2020. The manuscript from this study will be submitted to a severe asthma focused peer-reviewed scientific journal in due course.

7.0 Advisory group

ISAR Steering Committee Members	Country
Liam Heaney Andrew Menzies-Gow David Jackson Dermot Ryan Arnaud Bourdin	United Kingdom
Eric van Ganse Manon Belhassen	France
Peter Gibson Vibeke Backer Chin Kook Rhee	Australia Denmark South Korea
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8.0 Research team

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9.0 Timelines

Projected timeline for the study is as follows:

Action	Timeline
Protocol finalisation	Feb 2018
Data extraction & preparation	Feb. 2018 – Mar. 2019
Analysis	Mar 2019
Pilot Results	Mar 2019
First draft of paper	April 2019

10.0 References

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11.0 APPENDIX

Appendix: Abbreviations

ADEPT	Anonymous Data Ethics Protocols and Transparency committee
ATS	American Thoracic Society
BMI	Body Mass Index
EMR	Electronic Medical Record
ENCePP	European Network Centres for Pharmacoepidemiology and Pharmacovigilance
ERS	European Respiratory Society
FEV ₁	Forced expiratory volume in the first second
FeNO	Fractional exhaled nitric oxide test
FVC	Forced Vital Capacity
GINA	Global Initiative for asthma
ICS	Inhaled Corticosteroid
ISAR	International Severe Asthma Registry
LABA	Long-Acting β -adrenoreceptor
LAMA	Long-Acting Muscarinic Antagonist
LTRA	Leukotriene Receptor Antagonist
OPCRD	Optimum Patient Care Research Database
QOF	Quality Outcomes Framework
RDAC	Risk Domain Asthma Control
REG	Respiratory Effectiveness Group

11.1 Appendix: Asthma READ codes



cl_asthma_qof.csv

Ref: <https://app.smartsheet.com/sheets/VxWpCPmhPwcMvf7RWF9F9j8VfG9RV9J3FjwMm9J1?view=grid>
Row 10 - OPRI_CL_ASTHMA_QOF_READCODES_V1.0

11.2 Appendix: Asthma medications



Appendix 11.4 -
dl_all_asthma_drugs.

11.3 Appendix: Excluded Respiratory morbidity READ codes



Appendix 11.5 -
160513_Read code list

11.4 Appendix: READ codes showing a referral to secondary care



cl_hospital.xlsx

11.5 Appendix: READ codes showing medium/high dose ICS



Appendix 11.7 -
ICS_LABA_ICSLABA_

11.6 Appendix: READ codes showing primary care exacerbation



Appendix 11.8 -
Exacerbation Read Codes (List to be reviewed)

11.7 Appendix: READ codes showing OCS



Appendix 11.9 -
170110_Read codes

11.8 Appendix: READ codes showing antibiotics





Appendix 11.10 -
160704_Read code list

11.9 Appendix: READ codes showing respiratory infections



Appendix 11.11 -
160512_Read codes list

11.10 Appendix: Codes showing poor asthma control

RCP Scores	 cl_rcp_scores.xlsx
Primary care exacerbation	See appendix 11.8 above
SABA Medications (not combinations)	 Appendix 11.12 - 160413_Read code list

11.11 Appendix: Codes showing invasive ventilation



Appendix 11.13 -
Invasive Ventillation - (List to be reviewed)

11.12 Appendix: Codes for comorbidities of interest



Appendix 11.14 -
Comorbidity Codes.xlsx (List to be reviewed)