Study protocol

# Demographic and Clinical Characteristics of Severe Asthma Patients Worldwide.

*Describing the demographic and clinical characteristics of an international cohort of adult severe asthma patients.*

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|---|---|
| **TITLE** | Demographic and Clinical Characteristics of Severe Asthma Patients Worldwide |
| Subtitle | Describing the demographic and clinical characteristics of an international cohort of adult severe asthma patients |
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| Marketing authorisation number | N/A |
| Study aims and objectives | Aim: Highlight the demographic and clinical features of severe asthma patients internationally<br><br>Objectives: Descriptively compare severe asthma populations between regions and countries |
| Country of study | Singapore, United Kingdom |
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# Contents

## 1.0 Background

Asthma is a chronic airway disease, which can vary from mild to very severe[1], and is rapidly becoming a significant source of morbidity and mortality worldwide[2]. Patients who suffer from the severe form of this disease are estimated to represent 5-10% of the total asthmatic population[3-5]. Although they represent a minority of patients with asthma, they present a challenge due to the extensive evaluation they require, insufficient evidence regarding personalised treatments, and their high health care resource burden.

Severe asthma is currently defined as “asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming ‘‘uncontrolled’’ or that remains ‘‘uncontrolled’’ despite this therapy” by the European Respiratory Society (ERS) and American Thoracic Society (ATS) task force[6]. A major challenge faced when determining the exact prevalence and phenotypes of severe asthma is the lack of a universally accepted definition of the disease. Many countries have definitions that are reflective of their unique clinical guidelines. This has led to the establishment of isolated severe asthma registries[7-9] Using an international registry of severe asthma patients that has pooled diverse data from across the globe will significantly increase the ability to ascertain actual severe asthma demographic and clinical characteristics according to a standardised globally accepted definition of the disease.

Demographic and clinical risk factors of severe asthma, including ethnicity and age of onset of asthma, have been reported in a country or region specific manner[10-12]. The global prevalence of such factors or similar attributes is unknown. This is the first effort to descriptively aggregate demographic and clinical characterisitics of severe asthma internationally.

Comparing and contrasting the current prevalence and potential risk factors of severe asthma worldwide, as well as between regions and/or countries, will heighten clinical, health economic, and regulatory understanding, as well as improve control of the disease.

### 1.1 Study aims

To inform the asthma scientific community of the demographic and clinical characteristics of severe asthma patients seen at severe asthma centres across the globe. This will help drive the next key research questions to be asked at the country, region, and international level.

### 1.2 Study objectives

**Primary objective**: To describe the global severe asthma population using aggregate demographic and clinical measures enumerated in section 4.0.

**Secondary objective**: To descriptively compare the distribution of demographic and clinical attributes of severe asthma patients across sub-populations (regions/countries).

## 2.0 Study design

### 2.1 Study design

This ecological study design is the first step to describe the severe asthma population and sub-populations using known measures of severe asthma epidemiology. A selective list of demographic and clinical variables from the International Severe Asthma Registry will be utilized to descriptively illustrate between country and region differences and similarities.

### 2.2 Inclusion criteria

The following inclusion criteria is used to enrol severe asthma patients into International Severe Asthma Registry (ISAR) and therefore this study.

| **Inclusion criteria** |
|---|
| • Patients 18 years or older<br>• Patients receiving treatment according to GINA step 5 ot uncontrolled at Step 4. Uncontrolled is defined as having severe asthma symptoms[1] or frequent exacerbations[2]. |

[1] **Severe asthma symptoms (ERS/ATS Guidelines)[13]:**
(a) Poor symptom control where Asthma Control Questionnaire consistently >1.5, Asthma Control Test <20 (or "not well controlled" by NAEPP/GINA guidelines)
(b) Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)
(c) Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year without clinical or laboratory data for concomitant respiratory infections.
[2] **Frequent severe asthma exacerbations (ERS/ATS Guidelines):**
Two or more bursts of systemic Corticosteroids (>3 days course each) in the previous year

### 2.3 Data source

Data for this study will be sourced from the International Severe Asthma Registry (ISAR).

The ISAR registry is a multi-country, multicentre, observational epidemiologic data repository, with retrospective and prospective data on severe asthma patients. 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. Data from from 14 countries, as defined by the inclusion criteria in section 4.1, feeds into ISAR. The time frame for the analyses will use data collected for the latest three years as of December 30th, 2017. This is to accomodate existing and new registries that have various dates of registry induction (baseline data capture).

This database has received a favourable opinion from the Health Research Authority for clinical research use (REC reference: 15/EM/0150).

ISAR has 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)[14].

## 3.0 Study variables and study outcomes

The following variables will be summarised in this study

### 3.1 Demographic variables

| Variable Name[3] | Description |
|---|---|
| Age<br>Gender<br>Height<br>Weight | Patient age in years, height measurement in metres (m) and weight measurement in kilograms (kg) |
| Body Mass Index (BMI) | Defined as the ratio of weight (kg) to squared height ($m^2$).<br>• 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 $kg/m^2$) and 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 mutiplied by the number of years smoked |

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

## 3.2 Clinical Variables

| Variable Name[3] | Description |
|---|---|
| ***ISAR Severe Asthma Criteria*** | |
| ISAR inclusion (GINA[4] guidelines) | Patient on GINA Step 5 treatment<br>OR<br>Patient on GINA Step 4 treatment with<br>(a) Severe asthma symptoms<br>(b) Severe asthma exacerbations requiring systemic corticosteroids |
| ***Medical History*** | |
| Age of asthma onset | Patient age in whole years or months (if less than 1 year) at which asthma symptoms began |
| Number of exacerbations | Count of exacerbations requiring rescue steroids in the past 1 year<br>• For analysis: continuous and categorical values (1,2,3,4 or more) |
| Number of invasive ventilations | Count of episodes of invasive ventilation ever prior to baseline. |
| Number of hospital admissions | Count of hospital admissions for asthma in the past 1 year |
| Number of emergency department admissions | Count of emergency department admissions for asthma in the past 1 year |
| Maintenance oral corticosteroids | Prescription of oral corticosteroids for maintainance |
| Asthma control | Categorised as controlled, partly controlled or uncontrolled according to the GINA Asthma Control Criteria |
| ***Blood and Sputum Tests*** | |
| Immunoglobulin E level | Counts of immunogloblin E, measured in kilounits per litre (kU/L) or international units per litre (IU/mL) |
| Blood eosinophil level | Counts of blood eosinophils, measured in cells per litre ($10^9$/L).<br>• Categorised as eosinophilic asthma (blood eosinophil level >0.3 x $10^9$/L) and non-eosinophilic asthma (blood eosinophil level <0.3 x $10^9$/L) |
| Sputum eosinophil level | Counts of sputum eosinophils, expressed as percentage (%) of the total cell count.<br>• Categorised as eosinophilic asthma (sputum eosinophil count >3%) and non-eosinophilic asthma (sputum eosinophil count <3%) |
| ***Allergy Testing*** | |
| Skin Prick Test | house dust mite (HDM), animal dander (cat, dog), pollen (tree, grass) and moulds (Aspergillus).<br>• Categorised as positive reaction if >3 mm is wheal diameter |
| Allergen-specific serum immunoglobulin E tests (ImmunoCAP, Enzyme-linked immunosorbent assay (ELISA), Radioallergosorbent test (RAST)) | IgE mediated allergy test |

[4] Global Initiative for asthma 2017: GINA Stepwise approach for asthma control

| | |
|---|---|
| | • Categorised[5] as Undetectable (<0.10kU/L), low (0.10-0.69kU/L), moderate (0.70-3.49kU/L), high (3.50-17.40kU/L), very high (17.40-49.0kU/L) |
| ***Spirometry*** | |
| Pre-bronchodilator FEV1 | Forced expiratory volume in the first second, measured in litres (L), before administering bronchodilator |
| Post-bronchodilator FEV1 | Forced expiratory volume in the first second, measured in litres (L), after administering bronchodilator |
| Pre-Bronchodilator FVC | Forced vital capacity, measured in litres (L) before administering bronchodilator |
| Post-Bronchodilator FVC | Forced vital capacity, measured in litres (L) after administering bronchodilator |
| Post-bronchodilator FEV1 (percentage of predicted) | Measured post-bronchodilator FEV1 as a percentage (%) of predicted FEV1 |
| Pre-bronchodilator FVC (percentage of predicted) | Measured pre-bronchodilator FVC as a percentage (%) of predicted FVC |
| Post-bronchodilator FVC (percentage of predicted) | Measured post-bronchodilator FVC as a percentage (%) of predicted FVC |
| Fractional exhaled nitric oxide ($FE_{NO}$) test | Measurements of fractional nitric oxide concentration in exhaled breath, measured in parts per billion (ppb) at a flow rate of 50mL/s<br>• Categorised as low $FE_{NO}$ (<25ppb) and high $FE_{NO}$ (>45ppb) |
| ***Comorbidity*** | |
| Allergic rhinitis | Allergic rhinitis diagnosis |
| Chronic rhinosinusitis | Chronic rhinosinusitis diagnosis |
| Eczema | Eczema diagnosis |
| Nasal polyps | Nasal polyps diagnosis |
| Atopic disease | Eczema or allergic rhinitis diagnosis |
| ***Medication*** | |
| ICS | Prescription for inhaled corticosteroid (ICS) |
| LABA | Prescription for long-acting β-adrenoreceptor agonist (LABA) |
| ICS+LABA | Prescription for inhaled corticosteroids and long-acting β-adrenoreceptor agonist (ICS+LABA) |
| LAMA | Prescription for long-acting muscarininc antagonist (LAMA) |
| Theophylline | Prescription for theophylline |
| LTRA | Prescription for leukotriene receptor antagonist (LTRA) |
| Anti-IgE | Prescription for Anti-Immunoglobulin E (Anti-IgE) |
| Anti-IL5 | Prescription for Anti-Interleukin 5 (Anti-IL5) |
| Macrolide Antibiotic | Prescription for Macrolide Antibiotic |
| Other Steroid Sparing Agent | Prescription for Other Steroid Sparing Agent |

## 4.0 Statistical analysis

Descriptive statistics will be provided for continuous and categorical variable accordingly:

[5] Categorization based on review article: Interpretation of IgE-Mediated Allergy Tests (RAST)

- 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-quantile range ($25^{th}$ and $75^{th}$ percentile)
- For categorical variable the summary statistics will include:
  - Sample size (n)
  - Range (if applicable)
  - Count and percentage by category (distribution)

## 4.1 Software used

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.

## 4.2 Significance testing

Country or region (group) comparison will be examined with contingency tables and group difference will be tested for statistical significance via Chi-square tests for comparison of counts. Moreover, t-test or one-way analysis of variance (ANOVA) will be applied to test for statistical significance for comparison of means across groups. Statistical significance will be defined as $p < 0.05$.

## 4.3 Group characterisation

### Demographic characteristics

Univariate distributions for patient characteristics (age, gender, ethnicity, smoking status (including pack years), and BMI) will be described for the overall population as well as by country.

### Clinical characteristics

**Severe Asthma Status**

Univariate distribution of patients receiving GINA Step 5 or uncontrolled on GINA Step 4 (asthma status) will be provided. The proportion of patients in each asthma status group will

be exemplified by the current type of therapy (biologic or maintenance corticosteroids or inhaled corticosteroids), average age of onset of asthma, and asthma control categories.

Distribution of the following clinical characteristics (e.g. lung function, Immunoglobulin E, comorbidities etc.) will be summarised for the overall global population and by country. Clinical characteristics such as Exacerbation, IgE, Comorbidites will be reported adjusting for severe asthma status, gender, age of onset. Immunoglobulin E will be reported by severe asthma status, gender (within variable strata for each variable will be derived as per Section 3.0).

**Comorbidities**

All five comorbidities listed in Section 3 will be described by:

- Age
- Gender
- Severe asthma status
- Age of onset of asthma
- Blood eosinophil levels

**Medical Management**

Number of patients on the following type of therapy by blood eosinophilic status and GINA asthma control status (see Section 3):

- Maintenance oral corticosteroids
- ICS
- LAMA
- Theophylline
- Leukotrine receptor antagonist
- Biologics (Anti-IL5 and Anti-IgE)
- Macrolide
- ICS + LABA
- ICS + LABA + LAMA
- ICS + LABA + LTRA
- Other steroid sparing agent

**Adherence to therapy**

Described by:

- Age
- Gender
- Severe asthma status
- Age of onset of asthma
- Asthma control status
- Eosinophilic status (blood and sputum)

**Past 12-month health care utilization (hospitalization admssions and emergency department), exacerbations, and invasive ventilation**

Number of visits or its categories by:

- Severe asthma status
- Age of onset of asthma
- Asthma control status
- Immunoglobulin E level
- Eosinophilic status (blood and sputum)

Further group combinations, beyond the bivariate relationships shown above, will be performed as well, conditional to data availability.

## 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.[14]

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 boads 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 utlised as an anonymized 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

Initial results from this study will be submitted in abstract form for ERS Meeting 2018 or ATS Meeting 2018. The mansucript from this study will be sumbitted to a severe asthma focused peer reviewed scientific journal in due course.

## 7.0 Advisory group

| **ISAR Steering Committee Members** | **Country** |
|---|---|
| Liam Heaney<br>Andrew Menzies-Gow | United Kingdom |
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## 9.0 Timelines

Projected timeline for the study is as follows:

| Action | Timeline |
|---|---|
| Protocol finalisation | 1 week |
| Data extraction & preparation | 4-6 weeks |
| Analysis | 3 weeks |
| First draft of paper | 4-6 weeks |

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# 11.0 APPENDIX

## 11.1 Appendix : Abbreviations

| | |
|---|---|
| ADEPT | Anonymous Data Ethics Protocols and Transparency committee |
| ATS | American Thoracic Society |
| BMI | Body Mass Index |
| ENCePP | European Network Centres for Pharmacoepidemiology and Pharmacovigilance |
| ERS | European Respiratory Society |
| FEV1 | Forced expiratory volume in the first second |
| FeNO | Fractional exhaled nitric oxide test |
| FVC | Forced Vital Capacity |
| GINA | Global Initiative for asthma |
| IgE | Immunoglobulin E level |
| ICS | Inhaled Corticosteroid |
| ISAR | International Severe Asthma Registry |
| LABA | Long-Acting β-adrenoreceptor |
| LAMA | Long-Acting Muscarininc Antagonist |
| LTRA | Leukotriene Receptor Antagonist |
| REG | Respiratory Effectiveness Group |