Study Protocol

ImPact of comoRbidity In Severe asthMa patients (**PRISM**)

Prevalence of comorbidities in adult patients with severe asthma and association with response to biologics

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Study aims and objectives	**Aim:** To understand the pattern of comorbidities in adults with severe asthma and investigate their association with asthma-related outcomes. **Objectives:** 1. To assess the prevalence of individual comorbidities and predefined comorbidity categories in severe asthma patients, and explore comorbidity co-occurrence; 2. To compare the comorbidity prevalence by demographic and clinical characteristics of severe asthma patients; 3. To determine the association between T2 comorbidities/comorbidity category and response to biologics.
Countries of study	Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Portugal, Saudi Arabia, South Korea, Spain, Taiwan, United Arab Emirates, United Kingdom, United States of America
Author(s)	Ghislaine Scelo

Contents

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ABPA	Allergic bronchopulmonary aspergillosis
ADEPT	Anonymous Data Ethics Protocols and Transparency
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
EGPA	Eosinophilic granulomatosis with polyangiitis
ENCePP	European Network Centres for Pharmacoepidemiology and Pharmacovigilance
FVC	Forced vital capacity
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in the first second
GERD	Gastro-oesophageal reflux disease
GINA	Global Initiative for Asthma
GPA	Granulomatosis with polyangiitis
IgE	Immunoglobulin E
IL-4, -5, -13	Interleukin-4, -5, -13
IL-4R, -5R	Interleukin-4 receptor, -5 receptor
ISAR	International Severe Asthma Registry
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
NERD	Nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease
NSAID	Nonsteroidal anti-inflammatory drug
OCS	Oral corticosteroids
OPC	Optimum Patient Care
OPRI	Observational and Pragmatic Research Institute
OSAS	Obstructive sleep apnoea syndrome
REG	Respiratory Effectiveness Group
T2	Type 2 inflammation

1.0 Background

Comorbid conditions – such as allergic rhinitis, gastro-oesophageal reflux disease (GERD), and obesity – are common in asthma (1). They are conditions or diseases that coexist with asthma and may have causal connection with asthma (2,3). The associated economic burden is substantial, with overall comorbidity-attributable healthcare costs five times higher than costs attributable to asthma alone, increased risk of work disability, and significant productivity losses (4–6). In addition, patients with comorbidities are at an increased risk of poor asthma-related outcomes (7,8).

Comorbidities can complicate asthma management in multiple ways: (i) they may share the same pathophysiological process as asthma (eg, rhinitis); (ii) they may mimic and/or exacerbate asthma symptoms (eg, GERD); (iii) treatment for comorbid conditions may affect asthma (eg, β-blockers for the management of cardiovascular disease, ocular hypertension or anxiety); and (iv) comorbidities may be the result of side effects of asthma-related treatment (eg, oral corticosteroids [OCS]) (1,9,10). The list of asthma comorbidities is extensive and heterogeneous. The following categories have been described:

- **Type 2 inflammatory (T2) comorbidities** – They share with type 2 asthma the same immunopathological hallmark, ie the production of key cytokines including interleukins (IL)-4, -5 and -13 by T-helper 2 cells and type 2 innate lymphoid cells (11). The most common are allergic rhinitis, eczema/atopic dermatitis, and nasal polyposis. Other potentially T2 comorbidities include allergic conjunctivitis, eosinophilic oesophagitis, food allergy, eosinophilic chronic rhinosinusitis, allergic bronchopulmonary aspergillosis (ABPA), eosinophilic granulomatosis with polyangiitis (EGPA), nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NERD), and urticaria.
- **Comorbidities that mimic or exacerbate asthma symptoms** – These can complicate the diagnosis and management of patients with asthma and lead to under- or overtreatment (1). They include ABPA and EGPA (both potentially T2-related), granulomatosis with polyangiitis (GPA), bronchiectasis, dysfunctional breathing, GERD, chronic obstructive pulmonary disease (COPD), vocal cord dysfunction/laryngeal obstruction, anxiety and depression (both potentially OCS-related), as well as rare conditions such as sub glottis stenosis.
- **Comorbidities potentially related to OCS exposure** – While not necessarily caused by OCS exposure in asthma patients, a dose-response relationship between OCS exposure and the following conditions has been documented (12–14): obstructive

sleep apnoea syndrome (OSAS), obesity, diabetes and insulin resistance, dyslipidemia, hypertension, cardio-/cerebrovascular disease, osteoporosis and osteopenia, peptic ulcers, cataract, glaucoma, anxiety, depression, chronic kidney disease, thromboembolism, adrenal insufficiency, skin atrophy, and pneumonia and other serious infections.

In two nationally representative samples of the United States and the United Kingdom, the proportion of asthma patients reporting having at least one comorbid condition was 54% and 63%, respectively (15,16). The prevalence of individual comorbidities may vary with age, sex, and asthma phenotype (1).

Severe asthma is defined as asthma that remains uncontrolled despite therapy or requires extensive therapy indicated in steps 4 and 5 of Global Initiative for Asthma (GINA) recommendations (17). Patients with severe asthma represent 3–10% of the total population of asthma patients and contribute disproportionately to asthma morbidity, mortality, and costs (18). The treatment regimen typically includes high-dose of inhaled corticosteroids combined with a long-acting β2-agonist, a leukotriene modifier or theophylline, long-acting muscarinic antagonists, and/or long-term OCS use (18). Severe asthma patients can also be eligible for biologic add-on therapies, most of which target type 2 inflammation (18).

Comorbidities in severe asthma are more common that in mild-to-moderate asthma, and multiple comorbidities may affect the same patient (10). Some comorbidities may be more common in specific phenotypes of severe asthma, although the evidence in this area is still limited, challenging the assessment and management of this patient group (9). Moreover, severe asthma patients with serious or multiple comorbid conditions are generally excluded from clinical trials, leading to a lack of strong evidence to guide asthma treatments in these individuals (1). Interestingly, the presence of T2-related comorbidities could predict a better response to biologics (19). Understanding the pattern of comorbidities by severe asthma phenotypes/endotypes and assessing their impact on response to asthma treatment is important to improve the assessment of comorbidities and asthma management.

The large, multi-country cohort of severe asthma adult patients included in the International Severe Asthma Registry (ISAR) constitutes a unique resource to investigate the impact of comorbidity in severe asthma. We propose to study the prevalence and patterns or comorbidities in patients enrolled in ISAR, and to assess the association between T2 comorbidities and response to biologics.

2.0 Study Aims and Objectives

2.1 Study Aims

To understand the pattern of comorbidities in adults with severe asthma and investigate their association with asthma-related outcomes.

2.2 Study Objectives

Objective 1: To assess the prevalence of individual comorbidities and predefined comorbidity categories in severe asthma patients and explore comorbidity co-occurrence.

- Comorbidity categories include: T2; mimicking/exacerbating asthma; potentially OCS-related.

Objective 2: To compare the comorbidity prevalence by demographic and clinical characteristics of severe asthma patients.

- The comparisons will focus on comorbidity categories, comorbidity counts, and common (≥10% prevalence overall) individual comorbidities.

Objective 3: To determine the association between T2 comorbidities/comorbidity category and response to biologics.

- Response to biologics measured through four outcomes in the period 24 weeks to 1 year following biologic initiation: exacerbation rate; asthma control; lung function; and total OCS dose.

3.0 Study Design

3.1 Study Population

ISAR is an international collaborative initiative to gather pseudonymous (de-identified), longitudinal, observational data for patients with severe asthma. Eligible participants are patients aged 18 years or more who visit a participating centre, have a diagnosis of severe asthma, and are willing to contribute with their data. Severe asthma is defined as asthma treated with 2018 GINA Step 5 or uncontrolled on GINA Step 4 treatment regimens. Willingness to participate is assessed through signing a written informed consent.

As of July 2021, ISAR holds standardized patient-level data for approximatively 11,300 patients from almost 300 clinical sites in 21 countries, including over 9,000 patients recruited prospectively during the period 2018-2021. Data relevant to severe asthma research are collected at each visit or extracted from medical records. This includes details on asthma phenotype and endotype, asthma-related outcomes, treatment regimens, and data on comorbidities.

3.2 Type of Study

Objectives 1 and 2 will follow a **cross-sectional design** over the timeframe covered by ISAR. Data collected on comorbidities at any time during the patient follow-up will be used to compute ever/never variables and perform a descriptive analysis.

Objective 3 will follow a **prospective cohort design** using date at first biologic initiation as baseline. In patients initiating biologics, we will measure the association between history of comorbidities at baseline and asthma-related outcomes in the period 24 weeks to 1 year following the biologic initiation.

3.3 Inclusion and Exclusion Criteria

In addition to ISAR eligibility criteria as described in point 3.1, the following criteria will apply:

Inclusion Criteria

<u>Objectives 1 and 2:</u>

- Available data on at least one comorbidity throughout the existing visits

<u>Objective 3:</u>

- Patients treated with biologics
- Available data on history of comorbidities at the time of first biologic initiation

Exclusion Criteria

Objectives 1 and 2:

- None

Objective 3:

- Use of biologics before enrolment date
- Having received bronchial thermoplasty
- Patients followed up for less than 24 weeks

4.0 Study Variables and Study Outcome Definitions

The study variables listed in tables 4.1 to 4.4 will be created using the ISAR database variables. They will be core or optional variables depending on whether the required ISAR variables form the core or bolt-on datasets of the registry. As of July 2021, bolt-on data is available for approximately half of the ISAR participants. Details are provided in table 4.5 and in section 6.

4.1 Comorbidity Variables

The ISAR core dataset contains four categorical and one continuous comorbidity-related variables:

- Indication of 1) eczema; 2) allergic rhinitis; 3) chronic rhinosinusitis; and 4) nasal polyps: current/past/never (as assessed by the clinician);
- Body mass index (BMI): calculated from the patient reported height and weight.

Data collected at each available visit will be used to compute binary variables (ever/never) for the four categorical variables and for obesity, defined as ever if BMI ever ≥30kg.m^{-2} and never otherwise.

The ISAR effectiveness bolt-on dataset (18 contributing countries) contains 15 binary (yes/no) comorbidity-related variables with associated date of start reported at each visit were relevant: 1) osteoporosis; 2) heart failure; 3) myocardial infarction; 4) stroke; 5) pulmonary embolism/venous thromboembolism; 6) glaucoma; 7) cataract; 8) renal failure; 9) depression; 10) anxiety; 11) T2 diabetes; 12) peptic ulcer; 13) pneumonia; 14) obstructive sleep apnoea; and 15) others.

Data collected at each available visit will be used to compute binary variables (ever/never) for the 14 specified conditions. In addition, the free text variables that accompanies the binary variable “others” will be used to identify patients with comorbidities not listed above but expected to be sufficiently prevalent in severe asthma to be routinely reported by clinicians, namely: allergic conjunctivitis; eosinophilic oesophagitis; food allergy; urticaria; ABPA; EGPA; NERD; bronchiectasis; dysfunctional breathing; GERD; emphysema; vocal cord dysfunction/laryngeal obstruction; dyslipidemia; hypertension; and adrenal insufficiency.

The ISAR safety bolt-on dataset (18 contributing countries) contains a binary variable (yes/no) that collect data on serious infections (ie, infections requiring hospitalization, invasive or non-invasive ventilation, intravenous antibiotics, or resulting in a fatal outcome) with associated

date of start reported at each visit were relevant. Data throughout the recorded visits will be used to compute a binary variable (ever/never) for serious infections.

Finally, the free text variable contained in the effectiveness bolt-on dataset will be scrutinized to identify potentially missed specified conditions depending on the data entry system adopted by participating countries.

Of note, for objective 3 where we will investigate the influence of comorbid conditions on response to biologics, data collected until baseline (initiation of biologics) will be used in principle to determine whether the patient is affected or not by the condition. However, we will consider using data from subsequent visits would this help recovering any missing data.

The following table provides a summary of the binary comorbidity variables that will be used for the analysis by categories of comorbidities.

Label	Type	Values	Core	Optional
Potentially T2-related comorbidities				
Eczema/allergic dermatitis	Binary	Ever, never	✓	
Allergic rhinitis	Binary	Ever, never	✓	
Nasal polyposis	Binary	Ever, never	✓	
Chronic rhinosinusitis	Binary	Ever, never	✓	
Allergic conjunctivitis	Binary	Ever, never		✓
Eosinophilic oesophagitis	Binary	Ever, never		✓
Food allergy	Binary	Ever, never		✓
ABPA[1]	Binary	Ever, never		✓
EGPA[1]	Binary	Ever, never		✓
NERD	Binary	Ever, never		✓
Urticaria	Binary	Ever, never		✓
Mimicking/exacerbating asthma comorbidities				
Bronchiectasis	Binary	Ever, never		✓
Dysfunctional breathing	Binary	Ever, never		✓
GERD	Binary	Ever, never		✓

[1] Can also mimic asthma.

COPD	Binary	Ever, never		✓
Vocal cord dysfunction/laryngeal dysfunction	Binary	Ever, never		✓
Anxiety[2]	Binary	Ever, never		✓
Depression[2]	Binary	Ever, never		✓
Potentially OCS-related comorbidities				
Obesity	Binary	Ever, never	✓	
Osteoporosis	Binary	Ever, never		✓
Heart failure	Binary	Ever, never		✓
Myocardial infarction	Binary	Ever, never		✓
Stroke	Binary	Ever, never		✓
Unspecified cardiovascular disease	Binary	Ever, never		✓
Pulmonary embolism/venous thromboembolism	Binary	Ever, never		✓
Hypertension	Binary	Ever, never		✓
Dyslipidemia	Binary	Ever, never		✓
Glaucoma	Binary	Ever, never		✓
Cataract	Binary	Ever, never		✓
Renal failure	Binary	Ever, never		✓
T2 diabetes	Binary	Ever, never		✓
Peptic ulcer	Binary	Ever, never		✓
Obstructive sleep apnoea syndrome	Binary	Ever, never		✓
Adrenal insufficiency	Binary	Ever, never		✓
Pneumonia	Binary	Ever, never		✓
Other serious infections	Binary	Ever, never		✓

4.2 Demographic Covariates

Label	Type	Values	Core	Optional
Age	Numerical	-	✓	
Sex	Nominal	Male, female	✓	

[2] Can also be OCS-related.

Ethnicity	Nominal	Caucasian, South East Asian, North East Asian, African, Mixed, Other, Unknown	✓
Country	Nominal	Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Korea, Kuwait, Mexico, Portugal, Saudi Arabia, Spain, Taiwan, United Arab Emirates, United Kingdom, United States of America	✓
Smoking status	Ordinal	Current smoker, ex-smoker, never smoked	✓

4.3 Clinical Covariates

Label	Type	Values	Core	Optional
Asthma clinical characteristics				
Age-of-asthma onset	Numerical	-	✓	
Number of exacerbations requiring rescue steroids within the last year	Numerical	-	✓	
Lung function: post-bronchodilatator FEV_1 (% predicted)	Numerical	-	✓	
Lung function: ratio of forced expiratory volume in 1 second over forced vital capacity (FEV_1/FVC)	Numerical	-	✓	
Asthma control assessment (as defined by GINA 2018 update)	Ordinal	Well controlled, partially controlled, not controlled	✓	
Long-term OCS use	Binary	Yes, no	✓	
Asthma biomarkers				
Blood highest eosinophil count within the last year (10^9 cells/L)	Numerical	-	✓	
Fractional exhaled Nitric Oxide (FeNO) test result (parts per billion [ppb])	Numerical	-	✓	
Count of blood IgE (IU/mL)	Numerical	-	✓	
Positive allergens to serum allergen or skin prick tests	Binary	Ever, never	✓	

Treatment regimen			
Dose of long-term OCS	Numerical	-	✓
Long-acting muscarinic antagonist (LAMA)	Binary	Yes, no	✓
Theophylline	Binary	Yes, no	✓
Leukotriene receptor antagonist (LTRA)	Binary	Yes, no	✓
Biologics anti-IgE	Binary	Yes, no	✓
Biologics anti-IL5/IL-5R	Binary	Yes, no	✓
Biologics anti-IL4/IL-4R	Binary	Yes, no	✓
Macrolide antibiotic	Binary	Yes, no	✓
Other steroid sparing agents	Binary	Yes, no	✓

4.4 Asthma-Related Outcome Variables

Label	Type	Values	Core	Optional
Exacerbation episodes in the period 24 weeks to 1 year after biologic initiation	Discrete	-	✓	
Asthma control assessment in the period 24 weeks to 1 year after biologic initiation (as defined by GINA 2018 update)	Ordinal	Well controlled, partially controlled, not controlled	✓	
Lung function: post-bronchodilatator FEV_1 (% predicted)	Numerical	-	✓	
Lung function: ratio of forced expiratory volume in 1 second over forced vital capacity (FEV_1/FVC) in the period 24 weeks to 1 year after biologic initiation	Numerical	-	✓	
Total dose of OCS in the period 24 weeks to 1 year after biologic initiation	Numerical	Dose X Frequency X Duration of use in maintenance OCS and rescue steroids	✓	

4.5 Meta-data Variables

ISAR central dataset aims to harmonise data collected by many severe asthma registries worldwide. Some participating countries contribute data through a standardized, fit-for-

purpose data entry system (OpenClinica platform), whereas others contribute through existing local registries using their own data collection tools and databases. In addition, some countries have been specifically contracted to provide bolt-on data whenever possible. These variations may result in data quality and completeness heterogeneity. The following meta-data variables will be used to examine this issue and to select sub-groups of participants for specific analysis.

Label	Type	Values
Data provided through OpenClinica data collection platform	Binary	Yes/no
Contracted for the collection of effectiveness bolt-on data	Binary	Yes/no
Contracted for the collection of safety bolt-on data	Binary	Yes/no
Recruiting clinical site	Nominal	-

5.0 Statistical Analysis

5.1 Objective 1

Overall prevalence of history of individual comorbidities (ever/never) will be calculated over the timeframe covered by ISAR. In addition, the number of comorbidities will be calculated for each patient and prevalence of comorbidity counts computed (e.g., prevalence of 0, 1, 2, and 3+ comorbid conditions). Finally, the prevalence of having at least one comorbidity in each category (potentially T2; mimicking/exacerbating asthma; potentially OCS-related) and at least one comorbidity in two and three categories will be calculated.

5.2 Objective 2

For individual comorbidities with overall prevalence ≥10%, comorbidity counts, and comorbidity categories, the prevalence will be compared between demographic and clinical features:

- Through chi-square tests for categorical variables: sex, ethnicity, country, smoking status, asthma control assessment, long-term OCS use, and asthma treatment regimen;
- Through t-test comparisons for continuous variables: age, age-of-asthma onset, number of exacerbations requiring rescue steroids within the past year, lung function, FeNO test results, count of blood eosinophil cells, and count of blood IgE. Where data are not normally distributed, non-parametric Wilcoxon test will be used instead of t-test.

For relevant continuous variables, categories will also be tested using clinically relevant thresholds: FeNO test (<25, 25~<50, ≥50 ppb); lung function (FEV_1/FVC: <0.70; ≥0.70); and age-of-asthma onset (<12; ≥12 years old).

5.3 Objective 3

Univariate analysis: For patients initiating biologics, we will compare four asthma-related outcomes between patients with at least one T2 comorbidity or without T2 comorbidity, and by individual T2 comorbidity types. Outcomes will be measured in the period 24 weeks to 1 year following the biologic initiation. We will apply different statistical tests depending on the outcome:

- **Exacerbation rate**: mean exacerbation frequency will be calculated from available data in the window of interest and compute as the number of exacerbation episodes per year on average. Rates will be compared with risk ratios.

- **Asthma control**: asthma control is assessed through three categories: well controlled; partially controlled; not controlled. The distribution of this variable will be compared between comorbidity groups using chi-square tests.
- **Lung function**: as described in point 4.4, lung function is assessed through a continuous variable using t-test or Wilcoxon test as appropriate.
- **Cumulative OCS dose**: the cumulative dose of OCS in the window of interest will be compared between comorbidity groups using t-test or Wilcoxon test as appropriate.

Multivariable analysis:

Multivariable models for specific asthma-related outcomes: post-biologic asthma-related outcomes (outcome variables) will be individually modelized with comorbidity variables (exposure of interest) and demographic/clinical covariates (potential confounders). We will use negative binomial regression for exacerbation rates, ordinal logistic regression for asthma control, and linear regression for lung function and cumulative OCS dose.

Secondary analyses:

1) Where numbers allow, the analyses will be stratified by biologic types.

2) Qualitative outcome variables will be tested using time-to-event analyses, starting at the end of the 24th week after biologics initiation:

- Exacerbation: time to first exacerbation (participants: all eligible patients);
- Asthma control: time to improvement of at least one stage (participants: uncontrolled and partially controlled patients);
- Lung function: time to ≥25% improvement of FEV_1 percentage of predicted (participants: patients with baseline FEV_1%<70%);
- OCS use: time to decreasing daily dose to 5mg or less (participants: patients who use more than 5mg OCS per day at baseline).

5.4 Software

The analysis will be conducted with SAS and R.

6.0 Feasibility and Anticipated Difficulties

The ISAR is a dynamic database that is continuously scrutinized for data quality for new participating sites and for new follow-up visits. It is formed of core and optional variables. A selection of T2 comorbidities, as well as obesity, are part of the core variables, while data for other comorbidities is optional. As of July 2021, a total of **11,383 participants eligible to objectives 1 and 2 (preliminary number)**. As many comorbid conditions were reported as common in previous studies of smaller size, we anticipate adequate statistical power for the univariate descriptive and comparison analysis foreseen for objectives 1 and 2. A detailed description of the prevalence by countries and sites, as well as across follow-up visits, will however be a pre-requisite to ensure data reliability and consistency. Exclusion from the analysis will be considered would any site or country show unexpected distributions of individual comorbidities.

Except for the core variables, available for the majority of participants, data on other comorbidities listed in table 4.1 pertains to the bolt-on datasets. Out of the 21 participating countries, 18 have been specifically contracted for the collection of bolt-on datasets but data is not available for all patients or for all variables at this stage. Non-contributing countries (overall or for specific variables) will be excluded from the analysis for relevant comorbid conditions. We will compare the distribution of covariates for included and excluded countries to evaluate the potential selection bias resulting from the lack of bolt-on data in some countries. Efforts will be made to ensure sufficient statistical power, for example by grouping comorbid conditions in larger categories, or removing from the co-occurrence analysis these conditions that show large numbers of missing data.

Demographic and clinical covariates will also be examined for missingness. While we do not anticipate large numbers of missing values as they belong to the core variables, ad-hoc contacts with participating sites might be required to solve any unexpected issues on specific variables. We do not plan to use imputation techniques for this study.

The number of patients with recorded “other” comorbidities is substantial. This is an ISAR free text variable that has required text mining techniques to identify comorbidities of interest for this study. The text mining exercise is close to completion, and we do not anticipate major difficulty in this area.

Finally, some countries contributing to ISAR have a focus on biologics patients, leading to an over-sampling of biologics patients in ISAR. We will examine the potential resulting bias by comparing the comorbidity distributions in biologics vs. non-biologics patients, adjusting for other covariates.

Objective 3 is focused on patients who initiated biologics. As of July 2021, these form a **subgroup of 4,732 patients (preliminary number)**. For objective 3 analysis, patients will have to be naïve of biologics at baseline and follow-up data for outcome will be necessary. Both conditions might lead to a substantial number of excluded patients, due to retrospectively enrolled patients for the former, and recently enrolled patients (short follow-up period) for the latter. Included and excluded patients will be compared for basic demographic and clinical variables to assess the potential selection bias resulting from the exclusions.

7.0 Regulatory and Ethical Compliance

This study was designed and shall be implemented and reported in accordance with the criteria of the "European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)" 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 ENCePP (www.encepp.eu).

ISAR is approved by the Health Research Authority for clinical research use, and governed by the Anonymised Data Ethics & Protocol Transparency (ADEPT) Committee. We will submit the finalised version of this protocol to the ADEPT committee (https://www.regresearchnetwork.org/adept-committee/) for approval.

All sites have entered 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 is hashed and has entered 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. This 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.

8.0 Data Dissemination

To our knowledge, our study will be the first international analysis of comorbidity in severe asthma patients. It will provide estimates for comorbidity prevalence using the largest severe asthma database available to date. The available numbers should allow to assess with confidence the associations between comorbidities and demographic and clinical features using an exploratory approach.

Results from the study will be submitted for publication in asthma focused peer-reviewed scientific journals. We will also consider submitting abstracts for distinct results to relevant international conferences. Authorship will follow the ISAR authorship policy.

9.0 Advisory Group

Professor David Price, Chief Investigator for the study, is the chair of the ISAR Steering Committee. Other members of the committee, as listed in the following table, will form the Advisory Group.

Project Steering Committee Member	**Country/Funder**
Jorge Maspero	Argentina
Mark Hew	Australia
Matthew Peters	
Peter G. Gibson	
George C. Christoff	Bulgaria
Todor A. Popov	
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11.0 Projected Timelines

Action	Timeline
Protocol finalisation	Aug 2021
Ethics approval	Sep 2021
Data extraction and preparation	Sep 2021
Analysis and preliminary results	Nov 2021
Study report	Dec 2021

12.0 References

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