Study Protocol

CLinical oUtcomes before and after biologic treatMent by bIologic class, by iNdividuAl biologic, and by subgroups of baseliNe characTeristics – (LUMINANT)

Descriptive analysis and characterization of clinical outcomes of patients with severe asthma before and after biologic treatment per class of biologic, individual biologic and subgroup of patients' baseline characteristics

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TITLE	**Clinical outcomes before and after biologic treatment by biologic class, by individual biologic, and by subgroups of baseline characteristics (LUMINANT)**
Subtitle	Descriptive analysis and characterization of clinical outcomes in patients with severe asthma before and after biologic treatment per class of biologic, individual biologic and subgroup of patients' baseline characteristics
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Study aims and objectives	1. Description of baseline characteristics of patients with severe asthma before biologic treatment initiation a. Overall b. By individual biologics c. By class of biologics d. By baseline characteristics of interest 2. Descriptive analysis of clinical response for patients with severe asthma after biologic treatment initiation a. Overall b. By individual biologics c. By class of biologics d. By baseline characteristics of interest 3. Identification of independent factors associated with clinical response in patients with severe asthma with biologic treatment 4. Comparison of those who responded to those who did not respond and to the whole ISAR cohort 5. Describe the overlap of response in different domains 6. Description of super-responders 7. Identify independent factors associated with response in different domains
Countries of study	TBD – subject to patients' data availability in the International Severe Asthma Registry
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Contents

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ADEPT	Anonymised Data Ethics & Protocol Transparency
ANOVA	Analysis of variance
ATS	American Thoracic Society
BEC	Blood eosinophil count
BMI	Body mass index
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
HDM	House dust mite
ICS	Inhaled corticosteroids
ICU	Intensive care unit
IgE	Immunoglobulin G
IL	Interleukin
ISAR	International Severe Asthma Registry
ISC	ISAR Steering Committee
LABA	Long-acting β_2-agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
MCID	Minimal clinically important difference
NA	Not applicable
OCS	Oral corticosteroids
OPC	Optimum Patient Care
OPRI	Observational and Pragmatic Research Institute
QoL	Quality of life
RCT	Randomised control trial
REG	Respiratory effectiveness group
ROC	Receiver operating characteristic
SAT	Serum allergen test
SPT	Skin prick test

SCS	Systemic corticosteroid
TBD	To be defined
T2	Type 2

1.0 Background

Asthma is a heterogeneous disease, characterized by airway inflammation. It is defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation[1]. There is more than 300 million people suffering from asthma and almost 0.5 million annual deaths worldwide[2]. An estimated 3 to 10% of asthmatic patients suffer from severe asthma, defined by the Global Initiative for Asthma (GINA) as asthma which is uncontrolled despite adherence with maximal optimized Step 4 or Step 5 therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased[1]. Severe asthma is associated with an increased risk of mortality and hospitalization, a reduced quality of life (QoL), and increased health care costs. While being a small proportion of the asthmatic population, patients with severe asthma contribute as much as 60% of the healthcare cost, representing a large economic burden on health system and society, and a high burden on patients and their family[3–5].

In the last decade, new innovative therapies targeting different aspects of asthma inflammatory pathways have been discovered and licensed[1]. While these biologic therapies have brought huge improvements to the treatment of people with severe asthma, significant knowledge gaps that could improve the real-world implementation and impact on patient care pathway remain. Indeed, the larger part of the body of evidence on efficacy and safety of these new drugs rely on randomised control trials (RCT). While being the gold standard in biological evidence and a pillar in the licensing process, RCT results are conducted on highly selected population under strict control conditions that may not be representative of patients behaviour in real life and of the population that could benefit from new treatments assessed[6–8]. In addition, multiple outcomes have been used to assess treatment efficacy, adding to the complexity of capturing the broad benefits treatments for different types of severe asthma patients[9].

Disease control in severe asthma is difficult to maintain and complex to assess. It is key to predict or understand very early which patients can benefit from available treatments[10]. It requires regular patient review by physicians to ensure accurate recording of asthma outcomes including assessment of symptoms, exacerbations, lung function, quality of life and other measures of control and future risk[11]. The measures of asthma control are wide-ranging and include objective measures such as lung function, biomarkers, and subjective measures reported by patients such as asthma symptoms and health-related quality of life[11,12]. Routine assessment represents an important source of information, especially for disabling conditions

requiring individualised therapies such as severe asthma. As such, participation in a registry or clinical trial are advocated for patients in international guidelines[11]. Registries are useful for investigating knowledge gaps in heterogeneous and rare diseases for which clinical trials can provide limited data, and are very important in assessing the real world value of novel (and often expensive) therapies. In particular, pooling larger and broader populations than seen in randomised controlled trials, registries can identify subgroups who do well or do not respond and to monitor safety especially for rare adverse events. Registries may capture epidemiologic characteristics of real world patients' populations, and allow hypothesis generation, formation of new evidence as well as capture of unmet needs[13].

Therefore, the aim of this study is to characterize the population of patients with severe asthma who has access to biologic treatment at baseline and after initiation of biologic therapies, and to identify those who are benefitting from them and factors that are associated with improvements in asthma-specific outcomes after biologic initiation. Using the International Severe Asthma Registry (ISAR) cohort, we will get information about real life practices and identify predictors of clinical outcome improvement in patients with severe asthma receiving add-on biologics treatment. The ISAR cohort is the largest and only international registry with patient level data on adults with severe asthma available globally[14].

2.0 Study Aims and Objectives

2.1 Study Aims

To describe the ISAR cohort who initiate biologic treatment and examine clinical outcomes at 12 months by biologic class, and subgroups of patients, and compare these to those not initiated on biologic medications (Figure 1).

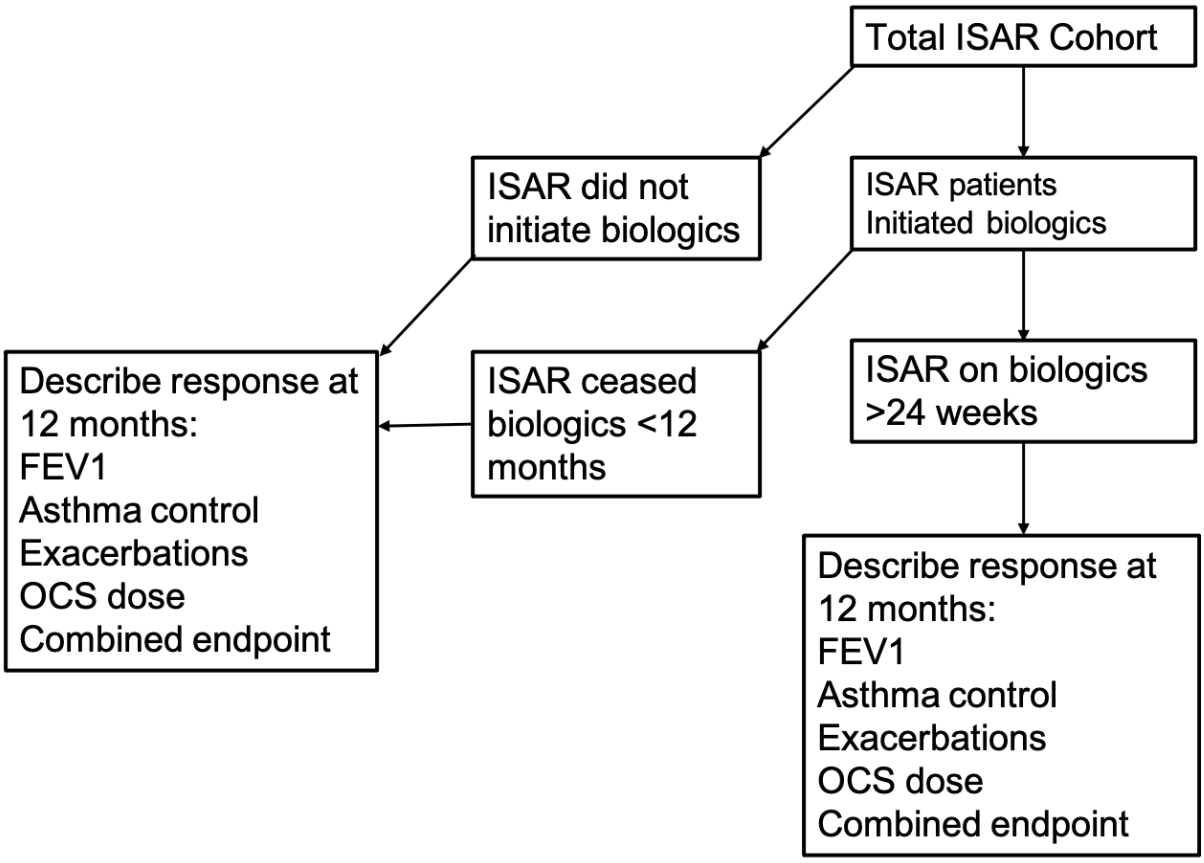


Figure 1: LUMINANT Study Flowchart

2.2 Study Objectives

Objective 1: Describe baseline characteristics of patients with severe asthma before biologic treatment initiation including demographics, asthma characteristics, medications, and asthma outcomes.

a) Overall
b) By class of biologics
c) Compared to the baseline demographics of the rest of the ISAR cohort

Objective 2: Describe the proportion and clinical characteristics of severe asthma patients who improve in each domain of asthma-specific outcomes as close to 12 months after biologic initiation as possible (a minimum of 24 weeks). Examine subgroups: class of biologics and population eligible for RCT. Domains of asthma-specific outcomes below:

a) Asthma control as measured by validated asthma-control questionnaire as controlled, partially controlled, or uncontrolled to be dichotomised into controlled and partially controlled versus uncontrolled.
b) Forced expiratory volume in 1 second (FEV_1) pre-bronchodilator (measured in litres) improvement >100mL or not
c) Reduced annualized rate of exacerbations, note: if initial annualised rate of exacerbations zero then excluded from this analysis
d) Reduced dose of chronic oral corticosteroids (OCS), note: excluded from this analysis if not on baseline chronic OCS

Objective 3: Compare the responders to the non-responders and to the ISAR cohort who did not initiate biologics including by presence of reversibility and biomarker gradient or expression.

Objective 4: Describe the overlap of response to each domain (Figure 2).

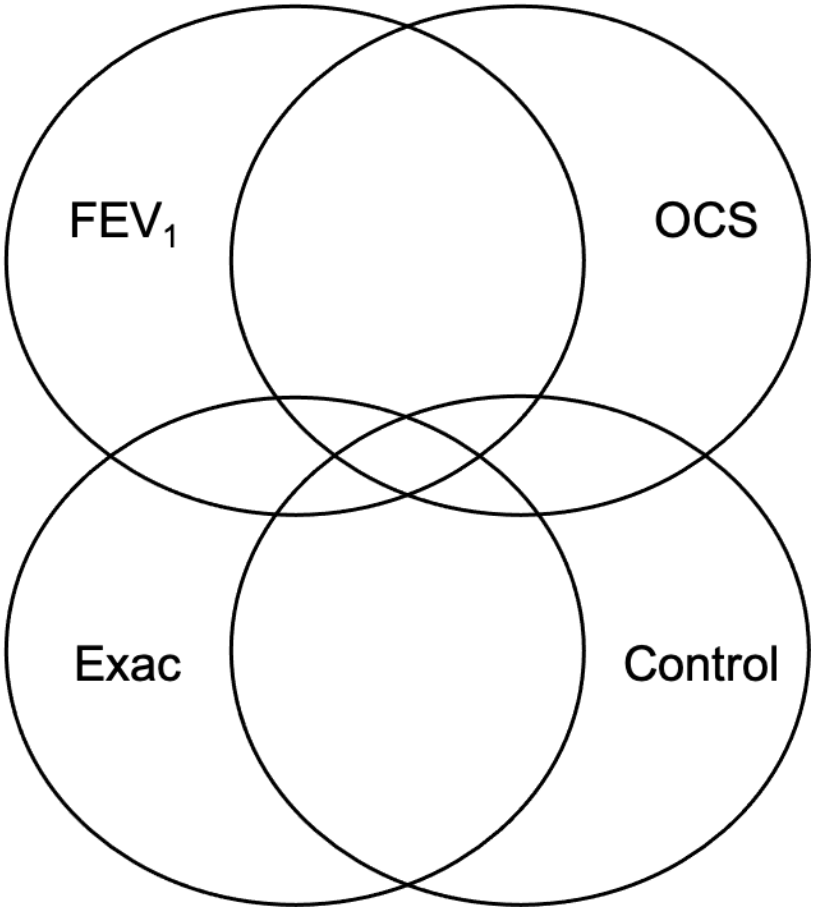


Figure 2: Overlap of response in each asthma-specific domain

Objective 5: Describe those who met a composite endpoint: a combination of FEV_1, exacerbations, chronic OCS reduction, and asthma control

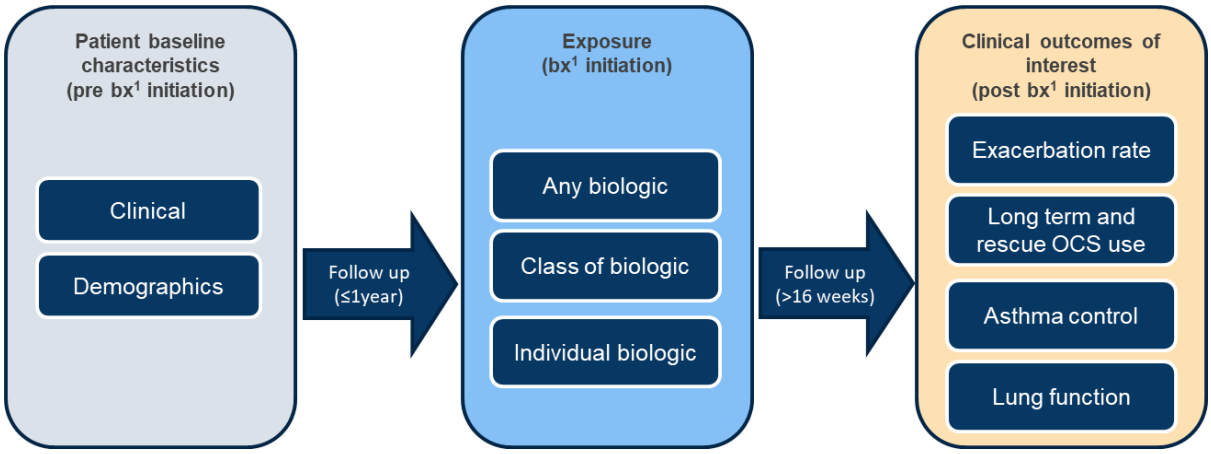
Objective 6: Describe super-responders

Objective 7: Identification of factors independently associated with response in patients with severe asthma receiving biologic treatment in asthma-specific outcomes:

a) Asthma control as measured by validated asthma-control questionnaire
b) FEV_1 pre-bronchodilator (measured in litres) change >100mL
c) Reduced annualized rate of exacerbations
d) Reduced dose of chronic OCS

3.0 Study Design

This is a registry-based longitudinal cohort study using a prospective international cohort of adult patients with severe asthma to characterize a real-world population treated with add-on biologic therapy and explore predictors of clinical response.



[1]Bx: biologic therapy

Figure 2: Study design and characteristics

4.0 Study Population

4.1 Data Sources

The data source is the ISAR registry[14], which is a multi-country, multi-centre, observational epidemiologic data repository, with retrospective and prospective data from >9,000 severe asthma patients. The key feature of the registry is its standardised data fields irrespective of data source. ISAR includes patient-level data from a combination of existing and new severe asthma registries, where primary data collection is mostly performed via eCRFs on a web-based platform. Registry data collection started in 2017 and is expected to continue up to May 2022 and beyond. Ethical governance for ISAR is 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)[15]. Anonymised person-level data from countries contributing data currently (Canada, USA, Mexico, Colombia, Argentina, the UK, Ireland, Denmark, Germany, Spain, Portugal, Greece, Italy, Bulgaria, South Korea, Japan, Taiwan, Singapore, Kuwait, the UAE, Saudi Arabia), will be used for this analysis, as defined by the inclusion criteria in section 4.2.

The study population include a subset of the ISAR population. Details of the ISAR registry have been published previously[16].

4.2 Inclusion and Exclusion Criteria

Inclusion Criteria

Eligible subjects are adults (≥18 years old) with severe asthma, defined as patients with uncontrolled asthma at GINA 2018 Step 4 or undergoing GINA 2018 Step 5 treatment at baseline, who have initiated a biologic after enrolment in ISAR, with at least 2 visits recorded, including a visit pre or at biologic initiation and 1 follow up visit post biologic treatment initiation (visit >24 weeks and closest to 1 year to be selected) in addition to ISAR registry inclusion criteria (Table 1).

Table 1: ISAR patient inclusion and exclusion criteria

Inclusion	Exclusion
Adult (≥18 years old) patients with severe asthma	

Inclusion	Exclusion
Undergoing GINA 2018 Step 5 treatment[a1] or Uncontrolled on GINA 2018 Step 4 treatment[1] Uncontrolled defined as at least one of the following (per American Thoracic Society (ATS)/ European Respiratory Society (ERS) guidelines[17]): • Poor symptom control: Asthma Control Questionnaire (ACQ) consistently >1.5, or Asthma Control Test (ACT) <20 (or 'not well controlled')[1] • Airflow limitation: Pre-bronchodilator FEV_1< 80% predicted, with reduced FEV_1/forced vital capacity (FVC) (defined as less than the lower limit of normal) • Serious exacerbations: ≥1 hospitalisation, intensive care unit (ICU) stay or mechanical ventilation in the previous year • Frequent severe exacerbations: ≥2 bursts of systemic corticosteroids with each course >3 days in the previous year	Lack of informed consent for participation

[a]Asthma controlled on high-dose inhaled corticosteroids (ICS)/long-acting β2-agonist (LABA) treatment was not part of the current inclusion for ISAR

ACQ*:* Asthma Control Questionnaire; ACT*:* Asthma Control Test; ATS*:* American Thoracic Society; ERS*:* European Respiratory Society; FEV_1: forced expiratory volume in 1 second; FVC*:* forced vital capacity; GINA*:* Global Initiative for Asthma; ICS*:* inhaled corticosteroids; ICU*:* intensive care unit; ISAR*:* International Severe Asthma Registry; LABA*:* long-acting β_2-agonist

Exclusion Criteria

Within ISAR patient population, the following patients will be excluded:

- Patients not receiving biologic treatment
- Patients who stopped biologic treatment before 24 weeks post initiation
- Patients with less than 24 weeks between biologic initiation and follow up visits

5.0 Study Variables and Study Outcome Definitions

The list of patients' variables collected in ISAR are available in Appendix 1. For this study, we will limit the analysis to the variables presented in the sections below.

5.1 Demographic and Clinical Characteristics

The demographic characteristics of the patients are listed in Table 2.

Table 2: Patients' demographic variables

Variable Name[1]	Description
Age Sex Height Weight	Patient age in years or category 18-64 y.o., 65-75 y.o., and ≥75 y.o. Gender (male or female) Height measurement in metres (m) Weight measurement in kilograms (kg)
Body Mass Index (BMI)	Defined as the ratio of weight (kg) to squared height (m^2) • Continuous variable • 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)
Ethnicity	Caucasian, Asian, African, Latino, Mixed, Other, Unknown
Country	Country of enrolment of the patients
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
Age at asthma onset	years
Altitude of residence	Meters above sea level as continuous variable or by ranges of altitude

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

5.2 Clinical Variables

The clinical characteristics of interest include usual biologics treatment criteria, asthma related outcomes, and other outcomes assessing:

- Background asthma therapy
- Lung function
- Asthma Control
- Exacerbations
- Healthcare resource use (unplanned primary care presentation, Emergency Department presentation, hospital admission, intensive care admission)
- Biomarkers (FeNO, blood eosinophil count (BEC), total immunoglobulin G (IgE), measures of atopy)
- Comorbidities
- OCS long term adverse events including BMI, osteoporosis, adrenal insufficiency, diabetes mellitus
- Other clinical outcomes (infection and anaphylaxis)

The clinical characteristics (Table 3) will be described at or before biologic initiation visit (T0) and at post biologic initiation visit (T1).

Table 3: Patients' clinical characteristics

Variable Name[2]	Description
ISAR Severe Asthma Criteria	
ISAR inclusion (GINA[3] guidelines)	Patient on GINA Step 5 treatment OR Patient on GINA Step 4 treatment with (a) Severe asthma symptoms (b) Severe asthma exacerbations requiring systemic corticosteroids
Medical History	
Asthma duration	Whole years or months (if less than 1 year) at which first asthma diagnosis/symptoms began to the date of biologic initiation

[2] All variables are measured at baseline; which will refer to the first patient visit where data is collected for ISAR
[3] Global Initiative for asthma 2017: GINA Stepwise approach for asthma control

Age of asthma onset	Age of first asthma diagnosis/symptoms
Number of exacerbations	Count of exacerbations requiring rescue oral corticosteroids in the past 1 year • For analysis: continuous and categorical values (1, 2, 3, 4, or more)
Adherence	Adherence to ICS/LABA Yes: Clinical Impression Yes: Prescription Records No: Not assessed or recorded
Number of invasive ventilations for severe asthma	Count of episodes of invasive ventilation ever
Number of asthma related hospital admissions	Count of hospital admissions for asthma in the past 1 year
Number of asthma-related emergency department visits	Count of emergency department admissions for asthma in the past 1 year
Asthma control	• Categorised as controlled, partly controlled, or uncontrolled according to the GINA Asthma Control Criteria/ACQ/ACT • Raw scores for ACQ and ACT so that minimal clinically important difference (MCID) may be calculated
Clinical management plan	Biologic therapy Bronchial thermoplasty Long-term oral corticosteroids Steroid sparing agent (e.g., methotrexate) Macrolide No data
Biologic time exposure	Time (days) from biologic initiation to visit T12 (post biologic) or date of stopping biologic treatment
Biologic treatment status at T1	Stopped or ongoing or switched

Time from biologic treatment to T1	Time (days) between biologic treatment stopped and T1
Follow up time	Time from T0 to T1
Biomarkers	
IgE level	Counts of IgE, measured in kilounits per litre (kU/L) or international units per litre (IU/mL)
BEC	Highest counts of blood eosinophils, measured in cells per litre (10^9/L).
Sputum eosinophil level	Highest counts of sputum eosinophils, expressed as percentage (%) of the total cell count.
Fractional exhaled nitric oxide (FeNO) test	Measurements of FeNO concentration in exhaled breath, measured in parts per billion (ppb) at a flow rate of 50mL/s Categorised as low FeNO (<50ppb) and high FeNO (≥50ppb)
Allergy Testing	
Skin Prick Test (SPT)	House dust mite (HDM), animal dander (cat, dog), pollen (tree, grass) and moulds (*Aspergillus*). • Categorised as positive reaction if ≥3 mm is wheal diameter
SPT positive allergens	Mould Mix, Dust Mite, Cat, Dog, *Aspergillus*, Animal Mix, Other • Categorised as positive reaction if >0.7kU/L
Serum Allergen Test (SAT)	Positive/Negative/No data
SAT positive allergens	Dust Mite (*e.g., D. Pteronyssinus*), cat hair, mould mix, dog hair, *Aspergillus*, other (Specified)
Spirometry	
Pre-bronchodilator FEV_1	FEV_1 measured in litres (L), before administering bronchodilator

Pre-bronchodilator FVC	FVC measured in litres (L) before administering bronchodilator
Post-bronchodilator FEV_1	FEV_1 measured in litres (L), after administering bronchodilator
Post-bronchodilator FVC	FVC measured in litres (L), after administering bronchodilator
Pre-bronchodilator FEV_1 (percentage of predicted)	Measured pre-bronchodilator forced expiratory volume in the first second ($FEV_{1)}$ as a percentage (%) of predicted FEV_1
Pre-bronchodilator FVC (percentage of predicted)	Measured pre-bronchodilator forced vital capacity (FVC) as a percentage (%) of predicted FVC
Post-bronchodilator FEV_1 (percentage of predicted)	Measured post-bronchodilator forced expiratory volume in the first second ($FEV_{1)}$ as a percentage (%) of predicted FEV_1
Post-bronchodilator FVC (percentage of predicted)	Measured post-bronchodilator forced vital capacity (FVC) as a percentage (%) of predicted FVC
FEV_1/FVC ratio pre-bronchodilator	
FEV_1/FVC ratio post-bronchodilator	
PC20 Methacholine/Histamine challenge test	Methacholine challenge test (also known as bronchoprovocation test) measured in mg/ml
Prevalent SCS-related Comorbidity[4]	
Anxiety/depression	Diagnosis for anxiety/depression
Osteoporosis	Diagnosis for osteoporosis
Diabetes	Diagnosis for diabetes
Peptic ulcer	Diagnosis for peptic ulcer
Pneumonia	Diagnosis for pneumonia
Obstructive sleep apnoea	Diagnosis for obstructive sleep apnoea
Renal failure	Diagnosis for renal failure
Serious infection	One or more serious infections (bacterial, viral, fungal, parasite)

[4] The time frame to collect comorbidity data is relatively short. Comorbidities with only substantial data will be analysed for this study.

Heart Failure	Diagnosis for indicated history of heart failure
Myocardial infarction	Diagnosis for myocardial infarction
Thromboembolism	Diagnosis for thromboembolism
Pulmonary embolism	Diagnosis for pulmonary embolism
Prevalent SCS-unrelated Comorbidity	
Allergic rhinitis	Diagnosis for allergic rhinitis
Chronic rhinosinusitis	Diagnosis for chronic rhinosinusitis
Eczema	Diagnosis for eczema
Nasal polyps	Diagnosis for nasal polyps
Cancer	Diagnosis for cancer
Medication[5]	
Long term OCS (Y/N, daily dose, duration)	Prescription of OCS for maintenance
Long-acting muscarinic antagonist (LAMA) (Y/N, duration)	Prescription for LAMA
Theophylline (Y/N, duration)	Prescription for theophylline
Leukotriene receptor antagonist (LTRA) (Y/N, duration)	Prescription for LTRA
Anti-IgE (Y/N, duration)	Prescription for anti-IgE: Omalizumab
Anti-IL5/IL5R (Y/N, type, duration)	Prescription for anti-Interleukin 5 (Anti-IL5): Mepolizumab, Reslizumab, Benralizumab
Anti-IL4Rα (Y/N, type, duration)	Prescription for anti-Interleukin 4Rα
Macrolide antibiotic (Y/N, type, duration)	Prescription for Macrolide antibiotics: Azithromycin, Clarithromycin, Erythromycin, Roxithromycin, Fidaxomicin, Telithromycin,
Other steroid sparing agent	Prescription for other steroid sparing agent (e.g., Methotrexate, Azathioprine, Cyclophosphamide, Mycophenolate Cyclosporine.)

5.3 Other variables

[5] All patients are assumed to be under ICS and LABA treatment, only additional treatments are listed

5.3.1 Biologic randomised clinical trial population – eligibility criteria

Studies assessing the external validity of efficacy RCT for severe asthma biologic therapies make the distinction between different categories of eligibility criteria: biomarker, diagnosis, and demographic. For the purpose of this study, we used eligibility criteria of drug specific pivotal phase 3 trials assessing efficacy on exacerbation or long term OCS usage, to assess the rates of real world patients fulfilling the most common eligibility criteria for their respective therapy drugs RCT[18–22].

Table 4: Severe asthma biologic efficacy randomised control trial main eligibility criteria[a]

Drug (Class)	Asthma Diagnosis	Asthma Treatment	Biomarker – BEC	Lung Function	Other
Exacerbation reduction					
Mepolizumab (IL-5)	TBD	TBD	TBD	TBD	TBD
Reslizumab[23] (IL-5)	ACQ-7 score ≥1.5	• ICS Medium • ≤1 controller	≥400 cells/µL	Airway reversibility: FEV_1 ≥12%	Age 12-75 y.o.
Benralizumab (IL-5R)	TBD	TBD	TBD	TBD	TBD
Dupilumab (IL-4/IL-13)	TBD	TBD	TBD	TBD	TBD
Omalizumab (IgE)	TBD	TBD	TBD	TBD	TBD
OCS reduction/withdrawal					
Mepolizumab[19] (IL-5)		• ICS High-dose ≥6 months • LTOCS ≥6 months • 1 Controller for ≥3 months OR history of 3 successive additional controller failure in the last 12 months	• ≥300 c/uL in the last 12 months OR • ≥150 c/uL in the last 3-8 weeks		
Reslizumab (IL-5)	TBD	TBD	TBD	TBD	TBD
Benralizumab[20] (IL-5R)		• ICS Medium – High dose LABA • LTOCS ≥6 months	≥150 c/uL	• Airway reversibility: FEV_1 ≥12% and 200 mL • Airway variability:	

				FEV_1 ≥20% between two consecutive clinic visits documented in the last 12 months	
Dupilumab[21] (IL-4/IL-13)	>1 year, GINA 2014	ICS High-dose ≥4 weeks SCS ≥6 months ≤2 controllers for 3 months		• Airway reversibility: FEV_1 ≥12% and 200 mL FEV_1 predictor ≤80%	
Omalizumab[22] (IgE)	GINA 3 or GINA 4				Age 12-75 y.o.

[a]Standard exclusion criteria
IL: interleukin

5.3.2 Clinical response

In order to identify patients' characteristics associated with clinical response, relationship between patients' demographic and clinical characteristics at baseline visit pre or at biologic initiation (T0) and clinical outcomes (cf. Table 5) reported at post-biologic visit (T1) will be explored. Clinical response (change from baseline) will be explored through:

1. The change from baseline in any clinical outcome meeting the definitions in Table 5 (see Table 5)[9]
    - Asthma control
    - OCS daily dose
    - Exacerbations
    - Lung function
    - Composite endpoint
2. Description of super-responders
3. Clinical response as defined in the publication under development by Perez et al looking at a composite definition of responder (see Table 6)[25].

Clinical response will be collected from the patients visit closest to a year post biologic initiation, with a minimum of 24-weeks of follow-up time post biologic initiation[11,26].

Clinical response from 4 categories of clinical outcomes will be explored (pending data availability):

- Asthma exacerbation, defined as:
    - Asthma-related hospital attendance/admission; AND/OR
    - Asthma-related A&E attendance; AND/OR

- An acute oral corticosteroid course of 3 days or more
- Separate recordings of exacerbations within 14 days of each other will be treated as the same exacerbation.

- OCS:
  - Long term OCS (LTOCS) dose defined prescription of daily dose for >1 month
  - Proportion stopping long term OCS
- Asthma control, 3 categories uncontrolled, partially controlled and controlled to be dichotomised into controlled and partially controlled or uncontrolled, defined as:
  - A combination of GINA, ACT and ACQ according to ISAR's site/country practices
  - % with controlled asthma at follow up
  - Change in category from uncontrolled to partially controlled/controlled
  - A subgroup analysis for those who have raw scores available for ACQ or ACT where those meeting the MCID for improvement will be considered responders
- Lung function, defined as:
  - Change in pre-bronchodilator FEV_1

Table 5: Clinical outcomes measure for clinical response assessment at post biologic initiation visit in patients with severe asthma

Variable Name[6]	Type	Description
Reduction in annual asthma exacerbations[7]	Rate (%)	• Reduction of 50% in number of exacerbations requiring rescue steroids between biologic initiation date and T1 • Number of exacerbations • Those who started with no exacerbations to be excluded
Total dose of oral corticosteroids during follow-up[8] • Long term use	Continuous/Categorical	Criteria: • Continuous: change in daily dose for those on daily OCS

[6] Outcome variables are measured in the follow-up visit after biologic initiation date
[7] Total number of exacerbations will be calculated between biologic initiation date and current visit date.
[8] If use of SCS started before the biologic initiation date, total dose will be calculated between biologic drug initiation date and end date of use/end of study. If use of SCS started after the biologic initiation date, total dose will be calculated between start- and end date of use/end of study

		• Reduction by 50% in oral corticosteroid dose • Categorical: cessation of daily OCS treatment
Asthma control in the past 4 weeks	Categorical	• Change from poor to partial or controlled on standard asthma control questionnaires • % achieving good control on standard asthma questionnaires • For those with raw scores available, those who met MCID for ACQ or ACT
Lung function	Categorical and continuous	• Increase in FEV_1 pre-bronchodilator by greater than or equal to 100mL from baseline • Change in FEV_1 pre-bronchodilator from baseline (litres)
Composite endpoint		• Based on a modified version of the Perez et al paper

Table 6: Definition of clinical response based on the composite score from Perez et al.

	Domains (criteria in order of importance for multiple options)			
Type of response	Exacerbation	OCS use	Asthma Control*	Lung Function
A score from 0 to 100 via multiple domains	<50% reduction ≥50% reduction, but ≥severe exacerbations No severe exacerbations	<50% reduction Reduction ≥50% but <100% Withdrawal	≥3 points for ACT Total score ≥20	Pre-BD FEV_1 increase ≥100mL FEV_1 ≥80% of predicted

** As ACT is not part of the ISAR variables, a proxy will be developed considering change in asthma control between uncontrolled, partially controlled and controlled*

5.4 Subset of interest

The clinical characteristics will be described for patients overall and per subgroup of:

- Biologic class:
  - Anti-IgE
  - Anti-IL5/5R
  - Anti-IL4/IL13
- Biologic individual drugs (ineligible *vs.* the RCT eligible population)
  - Omalizumab
    - Ineligible *vs.* eligible to RCT
  - Mepolizumab
    - Ineligible *vs.* eligible to RCT
  - Reslizumab
    - Ineligible *vs.* eligible to RCT
  - Benralizumab
    - Ineligible *vs.* eligible to RCT
  - Dupilumab
    - Ineligible *vs.* eligible to RCT
- Patients' characteristics of interest
  - LTOCS
  - Eosinophilic phenotype[27]
  - Presence of reversibility
  - T2 gradient
  - Combination of biomarker positivity

Other

5.5 Data management and data

5.5.1 Data management

TBD

5.5.2 Research dataset

TBD

5.5.3 Feasibility assessment

Completed.

6.0 Statistical Analysis

6.1 Software

SPSS Version 24 or R will be used to conduct all statistical analyses and data manipulations.

6.2 Descriptive Analyses

Overall and by subset groups (type of biologics, individual biologics and baseline characteristics), descriptive statistics for Section 5.1 Demographic Variables (Table 2) and Section 5.2 Clinical Variables (Table 3) will be provided for continuous and categorical variables accordingly:

Descriptive statistics for the overall population and by subgroup of interest:

- For variables measured on the interval or ratio scale, summary statistics produced will be:
  - Sample size (n)
  - Percentage non missing
  - Mean
  - 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)
- Characteristics of study groups will be compared and tested for statistical significance via McNemar's tests for comparison of counts data, t-test, or one-way analysis of variance (ANOVA) for continuous variables. Statistical significance will be defined as $p<0.05$.

6.3 Analytical Analyses

Data will be analysed using SPSS Version 24 according to a predefined data analysis plan to minimize bias. The analysis planned is presented below but will be further developed in a statistical analysis plan.

Characteristics associated with clinical response will be explored through 3 statistical models. The first model will consider patient demographic or clinical characteristics associated with any clinical response meeting the MCID (see Table 5), the second model will look at specific clinical response improvement defined by domain as in previous work conducted with the ISAR database[24], and the third model will be looking at clinical response as defined in the publication under development by Perez et. al looking at a composite definition of a responder score[25].

6.3.1 Model 1: Predictors of clinical response

Clinical response will be defined as a response in one or more of the 4 outcomes of interest. Response rate and its 95% confidence interval (CI) will be calculated for the patient's population. Logistic regression will be used to detect variables independently associated with response in each domain. Univariate analysis will be used to identify variables significantly associated with clinical response with a level of significance (p-value) <0.15.

The variable significant in univariate analysis, as well as known confounders of response (to be forced in the model even if p-value≥0.15), will be entered in a multivariate logistic regression model.

The final model will be:

$$P\left(Y = \frac{1}{0}\right) ij = \beta \times Patient\ Characterics + \mu \times country + \varepsilon$$

Where $P\left(Y = \frac{1}{0}\right) ij$ is the probability for a j patients from a i country to have a clinical response, the β are the fixed effects associated with patients' demographic and clinical characteristics at baseline, μ the country random effect and ε the error term.

The quality of the predictors identified in the model will be assessed through a receiver operating characteristic (ROC) curve and area under the ROC curve.

6.3.2 Model 2: Predictors of clinical response by domain

The statistical procedure as presented in section 6.3.1 will be implemented with clinical response define following the responder definition for Model A and clinical response in the domain of interest for model B:

- Model A: Responder vs non-responder
- Model B: Responder domain_k vs non-responder, where $_k$ is the individual domain of response from 1 to 4
- Model C: Responders vs rest of ISAR cohort
- Model D: Multinomial model for super responder

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 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 Optimum Patient Care (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

Results from this study will be submitted as abstracts to allergy or respiratory conferences. The manuscript from this study will be submitted to a severe asthma focused peer-reviewed scientific journal in due course.

9.0 Advisory Group

Professor David Price, Chief Investigator for the study, is the chair of the ISAR Steering Committee (ISC). 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
Eve Denton	Australia
Mark Hew	
John Upham	
Sinthia Bosnic-Anticevich	
Matthew Peters	
Peter G. Gibson	
Ceri Banks	
Chung, Li Ping	
Guy Brusselle	Belgium
George C. Christoff*	Bulgaria
Ted A. Popov*	
J. Mark FitzGerald	Canada
Mohsen Sadatsafavi	
Celine Bergeron	
Andréanne Côté	
Marie-Ève Boulay	
Hélène Villeneuve	
Mohit Bhutani	
Kenneth Chapman	
Carlos A. Torres-Duque	Colombia
Benjamin Sarta	
Patricia Parada	
Libardo Jiménez-Maldonado	
Mauricio Durán-Silva	
Leslie Vargas	
Bellanid Rodriguez	
Carlos Andrés Celis-Preciado	
Celeste M. Porsbjerg	Denmark
Charlotte S. Ulrik	
Johannes Martin Schmid	

Alan Altraja	Estonia
Lauri Lehtimäki	Finland
Arnaud Bourdin	France
Camille Taille	
Nicolas Roche	
Manon Belhassen	
Jérémy Charriot	
Christian Taube	Germany
Nikolaos Papadopoulos	Greece
Andriana I. Papaioannou	
Konstantinos Kostikas	
Sundeep Salvi	India
Richard Costello	Ireland
Breda Cushen	
Patrick Mitchell	
Deirdre Long	
Enrico Heffler	Italy
Giorgio Walter Canonica	
Concetta Sirena	
岩永賢司 Kenji Iwanaga	Japan
Mona Al-Ahmad	Kuwait
Désirée Larenas Linnemann	Mexico
James Fingleton	New Zealand
Sverre Lehmann	Norway
Piotr Kuna	Poland
João A Fonseca	Portugal
Alvaro Aranda	Puerto Rico
Riyad Al-Lehebi	Saudi Arabia
Mariko Koh	Singapore
Chin Kook Rhee	South Korea
Borja Garcia-Cosio	Spain
Luis Perez-de-Llano	
Rupert Jones	Sub Saharan Africa
Leif Bjermer	Sweden
David Aronsson	
Casper Winsnes	
Diahn-Warng Perng (Steve)	Taiwan

Hang Liang-Wen	
Chau-Chyun Sheu	
Erick Wan-Chun Huang	
Bassam Mahboub	UAE
Laila Salameh	
David Jackson	UK
Andrew Menzies-Gow	
John Busby	
Liam Heaney	
Paul Pfeffer	
Michael Wechsler	USA
Eileen Wang	
Amanda Grippen Goddard	
Arman Pirzad	
Trung N. Tran	AZ

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10.0 Research Team

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Observational & Pragmatic Research Institute (OPRI)

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Other OPRI Team Members:

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Senior Data Analyst: Anthony Newell [anthony@optimumpatientcare.org]

11.0 Timelines

Action	Timeline
Contract signature	April 2021
Literature search & proposal	April 2021
Proposal sign-off	May 2021
Full Protocol delivery	June 2021
Protocol sign-off	August 2021
Dataset delivery + ADEPT (if ISAR data is used) approval	September 2021
Analyses	November 2021
Final study report	December 2021
Study report sign-off	February 2022
Conference abstract	February 2022
Manuscript	April 2022

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13.0 APPENDICES

13.1 Appendix 1: Full list of ISAR 95 core variables[14]

Category	Variable field name	Recorded units
Blood/Sputum	Highest blood eosinophil count within the past year	Decimal number
	Date of the highest blood eosinophil count within the past year	DD/MM/YYYY
	Was this the highest blood eosinophil count during an exacerbation event?	No/Yes
	The highest blood eosinophil count within the past year and not during exacerbation	Decimal number
	Date of highest blood eosinophil count within the past year and not during an exacerbation event	DD/MM/YYYY
	Current blood eosinophil count	Decimal number
	Date of current blood eosinophil count	DD/MM/YYYY
	The highest sputum eosinophil count within the past year (percentage)	Decimal number
	Date of the highest sputum eosinophil count within the past year	DD/MM/YYYY
	IgE count	Decimal number
Diagnostics	Chest CT scan	Normal/Abnormal/Not done
	Date of chest CT scan	DD/MM/YYYY

	Bone densitometry (DEXA)	No/Yes
	Date of bone densitometry (DEXA)	DD/MM/YYYY
Lung function	Pre-bronchodilator FEV_1	Decimal number
	Post-bronchodilator FEV_1	Decimal number
	Pre-bronchodilator FVC	Decimal number
	Post-bronchodilator FVC	Decimal number
	Predicted FEV_1	Decimal number (auto-calculated)
	Pre-bronchodilator FEV_1 (% predicted)	Decimal number (auto-calculated)
	Post-bronchodilator FEV_1 (% predicted)	Decimal number (auto-calculated)
	Predicted FVC	Decimal number (auto-calculated)
	Pre-bronchodilator FVC (% predicted)	Decimal number (auto-calculated)
	Post-bronchodilator FVC (% predicted)	Decimal number (auto-calculated)
	FEV_1/FVC ratio pre-bronchodilator (%)	Decimal number (auto-calculated)
	FEV_1/FVC ratio post-bronchodilator (%)	Decimal number (auto-calculated)
	PC20 methacholine/histamine test	No/Yes
	Date of PC20 test	DD/MM/YYYY
	PC20 test result	Decimal number
	FeNO test	No/Yes
	Date of FeNO test	DD/MM/YYYY
	FeNO test result	Decimal number
Allergen testing	Environmental allergen test	Serum allergen test (CAP, ELISA, RAST)/SPT/not done
	Serum allergy test: Positive to perennial allergen	No/Yes

	Serum allergy test: Specify positive allergen and result	Dust mite (e.g. *D. pteronyssinus*)/grass mix/cat hair/mould mix/dog hair/Aspergillus/other (please specify)
	Date of serum allergy test	DD/MM/YYYY
	SPT: Positive to allergen	No/Yes
	SPT: Specify positive allergen and result	Grass mix/trees/weed mix/Aspergillus/mould mix/dust mite/food mix/animal mix/cat hair/dog hair/other (please specify)
	Date of SPT	DD/MM/YYYY
Asthma control[1]	GINA Asthma Control Questionnaire	
	In the past 4 weeks, did the patient have:	
	Daytime symptoms more than twice per week	No/Yes
	Any activity limitation	No/Yes
	Any nocturnal symptoms/awakening	No/Yes
	Reliever medication use more than twice per week	No/Yes
	Lung function (PEF or FEV_1) <80% of predicted or personal best	No/Yes
Asthma medication	Maintenance oral corticosteroids	No/Yes
	Start date of oral corticosteroids	DD/MM/YYYY
	ICS + LABA combination therapy	No Budesonide + Formoterol Fluticasone furoate + Vilanterol

		Fluticasone propionate + Salmeterol Fluticasone propionate + Formoterol Mometasone + Formoterol Beclomethasone + Formoterol Other
	Start/end date of ICS + LABA combination therapy	DD/MM/YYYY
	ICS (only)	No Triamcinolone acetonide Mometasone furoate Fluticasone propionate Fluticasone furoate Ciclesonide Flunisonide Budesonide Beclomethasone dipropionate Other
	Start/end date of ICS (only) therapy	DD/MM/YYYY
	LABA	No Formoterol Salmeterol Indacaterol Arformoterol Olodaterol Other
	Start/end date of LABA therapy	DD/MM/YYYY
	LAMA	No Aclidinium Tiotropium Umeclidinium Glycopyrronium

		Other
	Start/end date of LAMA therapy	DD/MM/YYYY
	Theophyllines	No Theophylline Aminophylline Other
	Start/end date of theophylline therapy	DD/MM/YYYY
	LTRA	No Zafirlukast Montelukast Other
	Start/end date of LTRA therapy	DD/MM/YYYY
	Anti-IgE treatment	No/Yes
	Start/end date of anti-IgE therapy	DD/MM/YYYY
	Anti-IL-5/IL-5R treatment, other	No Reslizumab Mepolizumab Benralizumab Other[2]
	Start/end date of anti-IL-5 therapy	DD/MM/YYYY
	Macrolide antibiotic treatment	No Azithromycin Clarithromycin Erythromycin Roxithromycin Fidaxomicin Telithromycin Other
	Start/end date of macrolide antibiotic therapy	DD/MM/YYYY
	Other steroid-sparing agents	Free text

Adherence	Evidence of poor adherence[3]	No Yes: Clinical impression Yes: Objective measures Yes: Prescription records
	Other factors contributing to severe asthma symptoms[4]	Free text
Management plan	Current clinical management plan[5]	Discharge to local service Optimisation of current treatment Biologic therapy (specific drug can be found in current medication) Bronchial thermoplasty Maintenance oral corticosteroids Steroid-sparing agent (specific drug can be found in current medication) Enter into clinical trial Other (please specify)

CAP immunoCAP test, *CT* computed tomography, *DEXA* dual energy X-ray absorptiometry, *ELISA* enzyme-linked immunosorbent assay, *FeNO* fractional exhaled nitric oxide, *FEV_1* forced expiratory volume in 1 second, *FVC* forced vital capacity, *GINA* Global Initiative for Asthma, *ICS* inhaled corticosteroids, *IgE* immunoglobulin E, *IL-5* interleukin-5, *ISAR* International Severe Asthma Registry, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *LTRA* leukotriene receptor antagonist, *PC20* provocative concentration of methacholine/histamine needed to produce a 20% decrease in FEV_1, *PEF* peak expiratory flow, *RAST* radio-allergosorbent test, *SPT* skin prick test.

[1]Asthma Control Questionnaire or the Asthma Control Test are optional extras for this category (depending on registry preference).

[2]Other new biologics will be added once approved and in use.

[3]Poor adherence to treatment can be indicated by selecting either (a) or (b):

- Clinical impression: opinion of a medical personnel
  E.g., i) Impression of 'non-persistence': patient stops taking medication.
  ii) Impression of 'non-conformation': patient does not take medication as prescribed.
- Prescription records: evidenced by medical records detailing prescriptions being issued and inadequately filled.
  E.g., Medication possession ratio (MPR) = (Sum of days' supply for all fills/Number of days) x 100% <80% threshold.

[4]Calls for a trained clinician's perception or opinion on any other external factors (if any) potentially contributing to the severe asthma symptoms.

E.g., weather (cold air), air pollution, physical activity (exercise-induced asthma symptoms), occupational triggers (workplace irritants, gases, chemical fumes, dust), strong smells (perfumes), prior respiratory infections.

[5]Aims to record the asthma action plan for a patient to review efficacy over time.

E.g., i) Entry into clinical trial: If patient can benefit from a clinical trial drug.
ii) Discharge to local asthma service: If patient has shown alleviated asthma symptoms
iii) Optimisation of current asthma therapy: If patient's current asthma therapy is titrated for better asthma management.

iv) Bronchial thermoplasty: If patient is eligible to have a surgery to manage their asthma.
v) Biologic therapy: If patient is prescribed biologic therapy.
vi) Others: Asthma education and inhaler use education.

13.2 Appendix 2: International Severe Asthma Registry bolt-on variables

Category	Variables
Safety	
Severe infection	Infection type Start and end dates Outcome of infection Site of infection
Malignancy	Malignancy history, type, stage, status, and diagnosis confirmation Start and end dates Outcome of malignancy Site of malignancy
Anaphylactic reaction	Likely exposure of the reaction Time to reaction Date of the reaction Outcome of the anaphylactic reaction
Effectiveness	
Comorbidities	Osteoporosis Osteoporosis: Start date Circulatory system disease Circulatory system disease: Type Circulatory system disease: Start date Glaucoma or cataract disease Ocular disease: Type Ocular disease: Start date Obstructive sleep apnoea Obstructive sleep apnoea: Start date Renal failure Renal failure: Start date

	Depression Depression: Start date Anxiety Anxiety: Start date Type II diabetes mellitus Type II diabetes mellitus: Start date Peptic ulcer Peptic ulcer: Start date Pneumonia Pneumonia: Start date
Dosage	Label dose for oral corticosteroids Frequency for oral corticosteroids Label dose for inhaled corticosteroids Frequency for inhaled corticosteroids
Exacerbation history	Dates of exacerbations indicated Type of rescue steroid used with label dose, frequency, start and end dates
Medication switching	Reason for switch in patient's asthma medication/treatment