Study Protocol

Assessing the impact of earlier access to biologics on remission and natural course of asthma (GLEAM)

An examination of the Association Between the Timing of Biologic Therapy Initiation, Disease Progression, and Remission Probability in Severe Asthma

Date:
25 April 2024

Client contact:
Trung N. Tran

OPC Global
5 Coles Lane
Oakington
Cambridge CB24 3BA
United Kingdom

OPRI Pte Ltd
22 Sin Ming Lane
#06-76, Midview City
Singapore 573969

Phone (UK): +44 1223 967855
Phone (SG): +65 3105 1489
Email: info@isaregistries.org
Website: http://isaregistries.org/

Chief Investigator:

Professor David Price, Professor of Primary Care Respiratory Medicine and OPRI Direct

Mobile: +44 7787905057

Office number: +44 2081233923

Skype ID: respiratoryresearch

Email: david@opri.sg

Project Coordinator:

Victoria Carter, Research & Operations Director

Observational & Pragmatic Research Institute

Office address: 22 Sin Ming Lane #06-76, Midview City, Singapore 573969

Direct number: +65 8650 8766

Email: victoria@opri.sg

Project Lead:

-

ISAR Steering Committee Lead:

David Price

Study Sponsor:

AstraZeneca

Primary Contact:

Trung N. Tran [trung.tran1@astrazeneca.com]

TITLE	**Assessing the impact of earlier access to biologics on remission and natural course of asthma (GLEAM)**
Subtitle	An examination of the Association Between the Timing of Biologic Therapy Initiation, Disease Progression, and Remission Probabilities in Severe Asthma
Protocol version number	V1.2
Medicinal product	Not applicable
Product code	Not applicable
Marketing authorisation holder	Not applicable
Marketing authorisation number	Not applicable
Study aims and objectives	**Study aims:** To evaluate the impact of early intervention with biologic therapies on the natural course of the disease in patients with severe asthma . **Study objectives:** **Objective 1**: To describe the timing of biologic therapy initiation using various definitions of time to initiation. **Objective 2**: To assess whether the timing of biologic therapy initiation is an explanatory factor in altering the natural history of asthma, including remission, biomarkers and individual clinical outcomes.
Countries of study	Argentina, Belgium, Brazil, Bulgaria, Canada, Colombia, Denmark, Estonia, France, Greece, India, Ireland*, Italy, Japan, Korea, Kuwait, Mexico, Norway, Poland, Portugal, Saudi Arabia, Singapore, Spain, Taiwan, United Arab Emirates (UAE), United Kingdom (UK), United States of America (USA)* *Awaiting final sign-off for contract extension (NJH and Beaumont)
Author(s)	Dr Alexandar Sterling, Lakmini Bulathsinhala, John Townend

Table of Contents

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADEPT	Anonymised Data Ethics & Protocol Transparency
ANOVA	Analysis of variance
BACs	Biologic Accessibility Criteria Score
BEC	Blood eosinophil count
BMI	Body mass index
FAO	Fixed airway obstruction
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in the first second
GEE	Generalised estimating equation
GINA	Global Initiative for Asthma
HD	High dose
IgE	Immunoglobulin E
ICS	Inhaled corticosteroids
IL-4, -5, -13	Interleukin-4, -5, -13
ISAR	International Severe Asthma Registry
ISC	ISAR Steering Committee
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
LTOCS	Long-Term Oral Corticosteroid
MD	Medium dose
OCS	Oral corticosteroids
OPC	Optimum Patient Care
OPRI	Observational and Pragmatic Research Institute
R	R software from the R Project for Statistical Computing
STATA	Stata software suite
FDA	U.S. Food and Drug Administration
EMA	European Medicines Agency
YLD	Years lived with disability

1.0 Background

Severe asthma represents a significant subset of the asthma population, characterised by its resistance to standard treatment options. Defined by the Global Initiative for Asthma (GINA) as asthma that either remains uncontrolled despite good adherence to high-dose treatments or requires such treatments to achieve adequate control, severe asthma affects 6.1% of all patients with asthma globally and generates a significantly higher per-patient economic burden than non-severe asthma[1,2]. Asthma accounts for over 1% of global Years Lived with Disability (YLDs), and its management is complex and multifaceted. Its disproportionate contribution to asthma morbidity significantly impacts healthcare systems, underlining the need for effective intervention strategies[3,4]. The weight of long-term side-effects of OCS, including obesity, diabetes, osteoporosis and fragility fractures, cataracts, hypertension, and adrenal suppression, as well as exacerbations, makes it necessary to strengthen the evidence regarding the timely initiation of biological therapies[2]. Biologic therapies, immunomodulatory drugs tailored to target specific components of inflammatory processes, have emerged as a breakthrough in severe asthma management over the last decades[5,6]. This cohort of therapies, which includes monoclonal antibodies against various cytokines, their receptors, and immunoglobulin E (IgE), have demonstrated efficacy in reducing exacerbation rates, improving or preservation of lung function, reducing/ceasing maintenance OCS use, increasing the likelihood of remission and enhancing the quality of life of patients with specific inflammatory phenotypes[6,7,8,9,10,23]. Medicine regulatory bodies including the Food & Drug Administration (FDA) and European Medicines Agency (EMA) have approved several biologics for therapeutic use in asthma, each predicated on evidence from clinical trials demonstrating their benefits in asthma patients[11,12]. However, RCTs usually include long-term severe asthma patients, thus, have not assessed the effect of the lag between diagnosis of severe asthma and the initiation of biologics in terms of clinical outcomes and/or remission.

Despite these advancements, managing severe asthma remains challenging due to the heterogeneous nature of the disease and variability in access, use and patient response to biological treatments[7,13,14,15]. This variability in response necessitates an exploration of factors that could predict and enhance treatment efficacy, particularly in the timing and selection of biologic therapies. The FULL BEAM study, as published in the American Journal of Respiratory and Critical Care Medicine, supports the hypothesis that early intervention with biologic therapy achieves better outcomes . It indicates that earlier intervention in terms of shorter duration of asthma predicts greater likelihood of achieving remission[16,24]. Early intervention is hypothesized to mitigate against the development of irreversible airway

remodelling, a critical determinant in long-term outcomes for severe asthma patients. This aligns with findings from other immune-mediated diseases, where early intervention can slow progression and improve remission rates[17]. Despite these findings, FULL BEAM also revealed several unanswered questions, including the optimal timing for initiation and the specific patient subgroups that might benefit most from early intervention and whether remission is maintained over time. These gaps underscore the need for further research to refine our understanding of how early intervention can be effectively implemented in routine clinical practice to maximize patient outcomes.

Understanding the optimal timing for initiating biologic therapies in severe asthma remains a crucial question that could significantly improve real-world clinical outcomes and reduce the socioeconomic burden of this disease. While previous studies have investigated the impact of asthma duration on biologic therapy initiation, there is a consensus that further investigation is needed to define what constitutes 'early' in the context of biologic initiation, and exactly how "timing" can be classified and approximated[18]. There are several possible factors that could influence the definition of 'early' versus 'late' initiation, such as the onset of severe asthma (early vs. later in life), and the predominant level of disease activity (poor lung function vs. severe exacerbations). Reaching an expert consensus on the definitions and proxies for timing and starting treatment is essential to guide research and develop tailored therapies for severe asthma. One source of variation lies in the eligibility criteria that is related to timely phenotyping and reimbursement criteria for initiating a biologic, between countries. Such differences can result in delays to treatment initiation for patients with similar disease manifestations (phenotypes) [19].

The International Severe Asthma Registry (ISAR) is a unique asset through which the effects of biologic therapy timing on disease progression and outcomes can be assessed. However, to enhance our understanding further, integrating data from the OPCRD[25] and CHRONICLE[22] will increase our study population, and provide the capability for additional proxies for severe asthma duration.

2.0 Study Aims and Objectives

Study Aims

To evaluate the impact of early intervention with biologic therapies on the natural course of the disease in patients with severe asthma .

Hypothesis: Earlier access to biologics changes the natural course of the disease of severe astham and chance of remission

Study Objectives:

Objective 1:

To describe the timing of biologic therapy initiation using various proxies of time to initiation

Objective 2:

To assess whether the timing of biologic therapy initiation is associated with the course of the disease in patients with severe asthma, including remission, biomarkers and individual clinical outcomes.

3.0 Study Design

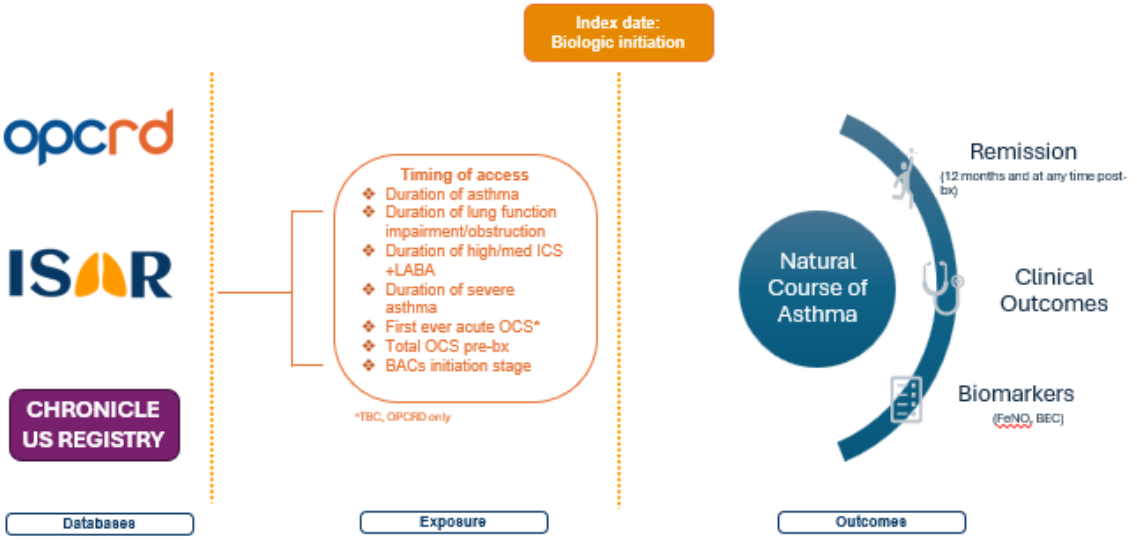

Figure 1 Study Design

BEC: Blood Eosinophil Count, OCS: Oral Corticosteroids, FeNO: Fractional Exhaled Nitric Oxide, LABA: Long Acting Beta Agonist, ICS: Inhaled Corticosteroid, BACs: Biologic Accessibility Score

This historical cohort study is designed to evaluate the impact of the association between biologic therapy initiation time and the natural course of asthma. By using a multi-centred approach via the international severe asthma registry (ISAR), the study will assess a set of clinical outcomes (including remission) and attributes (biomarkers) in patients, who receive biologic therapy at different times in their disease course. Biologic initiation date is the index date (objective 2), thus that initiation date starts the outcome period. For key aspects of the study design, please see Figure 1. For some time-to-biologic-initiation proxies, the earliest account of events, such as percent predicted FEV1 <80% or background therapy, may not be feasible, all continuous variables can be explored as categorical (yes|no) variables. Exposure proxies are outline in the below table 1.

Exposure Proxies:

Table 1 Proxies of biologic timing

	Proxy of timing	Type	Value[%]	Description
1	Duration of asthma from onset	Continuous	-	• Time from asthma onset to biologic initiation date
2	Duration of Lung function impairment/obstruction	Continuous	-	• Time from earliest pre-bx percent predicted FEV1 <80% to bx initiation OR • Time from earliest pre-bx, FEV1/FVC <0.70 (Fixed airway obstruction (FAO) as per GOLD criteria) to bx intiation • The earliest of the above proxies will take priority
3	Duration of severe asthma[22]	Continuous	-	• Time from start, or earliest high dose ICS with additional controllers (e.g. LABA, LAMA, LTRA, etc.) and biologic initiation, OR • Time from start, or earliest medium dose ICS + LABA and poor symptom control (uncontrolled, partly controlled) to biologic initiation • Time from start, or earliest medium dose ICS + LABA and 2 or more severe exacerbations (requiring OCS) to biologic initiation • Time from start, or earliest medium dose ICS + LABA and pre-bx, percent predicted FEV1 <80% to biologic initiation • The earliest of the above proxies will take priority.
4	Length of time since first requirement of frequent, acute OCS*[$]	Continuous	-	• Time from date of earliest, frequent (2+) acute OCS prescription to biologic initiation date (only in OPCRD) with a 24 month period • Will be explored as an interaction with ICS duration (OPCRD specific analysis)
5	Total OCS pre-biologic[$]	Continuous	-	• Total Pre-bx rescue and LTOCS exposure pre-bx iniation ○ Spread of total OCS exposure will be expolored ▪ 4 courses of OCS per year for 2 years, 2 courses of OCS per year for 4 years etc.
6	BACs[&]	Continuous	-	• Country specific biologic accessibility score. A composite score incorporates 10 prescription criteria, each with a maximum score of 10 points, per biologic. Referenced to European Medicines Agency marketing authorization specifications, a higher score reflects easier access[19]. • This will be used only in the country level ecological analysis per biologic.
7	BACs stage[&]	Categorical	Standard Late	• *Standard* – biologic initiation date is within 12 months of earliest date that eligibility criteria (country specific) as provided by the BAC survey. • *Late* – biologic initiation date is past 12 months of earliest date that eligibility criteria (country specific) met as provided by the BAC survey.

*OPCRD only

[&] based on the Biologic Accessibility Score, BACS,[19]

[%]Note: all continuous time duration variables can and will be assess as a continuous-categorical variable (e.g. 5, 10 year increments).

[$] OCS prescription given for other indication will be excluded (e.g. EGPA, MS)

4.0 Study Population

Data Sources

ISAR

The International Severe Asthma Registry (ISAR) is a global cooperative project designed to collect ongoing data from patients with severe asthma. To be included in this registry, patients must be 18 years of age or older, visit a participating centre, and have a diagnosis of severe asthma[20]. Additionally, they need to provide appropriate consent for their data to be used in ISAR research. Severe asthma is characterised either by its lack of control despite therapeutic efforts, or by the necessity for comprehensive treatment as described in steps 4 and 5 of the GINA guidelines[2]. Data collection began in 2018, and as of April 2024, there were **19,644** active participants from **25** countries enrolled into ISAR. Of these enrolled participants, at least 10,100 have initiated a biologic, and 6,854 are expected to provide ongoing prospective data (this number does not include the latest data cut and is therefore expected to increase by a significant margin). The data is comprised of relevant information collected from patients at each visit and extracted medical records. As of May 2024, there are over 3,200 patients that have initiated a biologic.

OPCRD

The Optimum Patient Care Research Database (OPCRD) collects and analyses anonymised primary care records from UK patients. Eligibility requires relevant medical histories from participating practices. The OPCRD, focusing on diseases like asthma and Chronic Obstructive Pulmonary Disease (COPD), captures data that reflect real-world treatment patterns, outcomes, and healthcare interactions in line with clinical guidelines. Since its inception in 2008, the OPCRD has compiled records from 26 million patients. The database features details on 2,047 patients prescribed biologics for severe asthma, with 1,704 providing longitudinal data for ongoing research.

CHRONICLE

CHRONICLE is a non-interventional, US, severe asthma registry that has collected data since February 2018. Adult (18 years or older) patients receiving a biologic or those who remain uncontrolled despite high-dosage inhaled corticosteroids and additional controllers are included in the registry. At inception, ISAR and CHRONICLE aligned on a core set of variables to allow for merging of a large study dataset. Like ISAR, CHRONICLE collects clinical outcome and patient reported outcomes every six months. As of March 2024, there were 2687 patients that were prescribed a biologic and had at least 12 months of follow-up data on remission domain (exacerbation, asthma control, LTOCS, lung function). CHRONICLE has up to 3 years of prospectively collected data on __4094____ patients[21].

Inclusion and Exclusion Criteria

Patients meeting the following minimum inclusion criteria will be included in this study

- Documented initiation of biologic therapy
- Age 18 years or older at the time of biologic initiation.
- Record of biologic initiation date
- Pre-biologic data

Patients with the following exclusion criteria will not be included in this study:

- Patients that have undergone bronchial thermoplasty

Study Variables

The following variables will be used to derive an analysis dataset suitable for the objectives of the study.

Patient Identifier and Demographic Variables

Label	Type	Values	Key	Core
Record ID	string	string	✓	
DOB	string	string	✓	
Biological Sex	string	Male, Female, Other	✓	
Height	numerical	numerical	✓	
Ethnicity	categorical	1, Caucasian | 2, South East Asian | 3, North East Asian | 4, African | 5, Mixed | 6, Other | 7, Unknown	✓	
Weight	numerical	numerical	✓	
BMI	numerical	numerical	✓	
Smoking status	Numerical	1. Current 2. Past		

		3. Never		
Body surface area (BSA)	numerical	numerical	✓	
History of Bronchial Thermoplasty	string	yes, no		✓

Diagnosis Variables

Label	Type	Values	Key	Core
GINA Asthma Control Assessment results available?	string	yes, no	✓	
On GINA Step 5 Treatment	string	yes, no	✓	
Uncontrolled on GINA step 4 treatment	string	yes, no	✓	
Uncontrolled defined as (a) Having frequent (2 or more) severe asthma exacerbations requiring oral corticosteroids per year	string	yes, no	✓	
Uncontrolled defined as (b) Having severe asthma symptoms	string	yes, no	✓	
Age at asthma onset	numerical	numerical		✓

Biomarker Variables

Label	Type	Values	Key	Core
Is the highest blood eosinophil count	string	yes, no	✓	
Unit of measurement for highest blood eosinophil count in period	string	string	✓	
Highest blood eosinophil count within the period	numerical	numerical	✓	
Date of highest blood eosinophil count within the period	string	string	✓	
FeNO test result	numerical	numerical	✓	
FeNO count within the period	string	yes, no	✓	
Date of FeNO test	string	string	✓	
~~Unit of measurement for blood IgE count~~	~~string~~	~~string~~	~~✓~~	
Blood IgE count within the period	numerical	numerical	✓	
Specific IgE positivity, serum or skin prick test	Categorical	yes, no		✓

Date of blood IgE count within the period	string	string	✓

Biologic Eligibility

Label	Type	Values	Key	Core
Biologic Start Date	string	string	✓	
Biologic Name	string	Omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, tezepelumab	✓	
Biologic eligible*	string	yes, no		✓
Date of Biologic eligibility*	string	string		✓

*eligibility is auto-calculated to show earliest date based on multiple key and core variables attributed to BACS criteria[18], national and manufacturer guidelines.

Defining Biologic Responsiveness/Remission

Label	Type	Values	Key	Core
Asthma control as defined by GINA, ACT, AIRQ, ACQ	categorical	Uncontrolled, Well- or Partly controlled	✓	
Date of spirometry result	string	string	✓	
Pre-bronchodilator FEV1 (actual or predicted %)	numerical	numerical		
Pre-bronchodilator FVC (actual or predicted %)	numerical	numerical		✓
Post-bronchodilator FEV1 (actual or predicted %)	numerical	numerical	✓	

Post-bronchodilator FVC (actual or predicted %)	numerical	numerical	✓	
FEV1/FVC ratio post bronchodilator (%) - Auto calculated	numerical	numerical	✓	
Date of Fractional Exhaled Nitric Oxide test	string	string	✓	
Was the Fractional Exhaled Nitric Oxide Test performed?	string	yes, no	✓	
Total number of severe exacerbations requiring rescue steroids past 12 months and same for 2 variables here below	numerical	numerical	✓	
Total number of hospital admissions for asthma	numerical	numerical	✓	
Total number of A&E attendances (Emergency room visit) for asthma	numerical	numerical	✓	
Total number of episodes of invasive ventilation ever	numerical	numerical		✓
Start and end date for each exacerbation	string	string	✓	
Start date of long-term oral corticosteroids	string	string		✓
Long-term OCS use + daily dose	string	string	✓	

Comorbidities

Label	Type	Values	Key	Core
Indication of: Nasal Polyps (NP)	string	yes, no	✓	
Indication of: Chronic Rhinosinusitis (CRS)	string	yes, no	✓	
Indication of: CRS +/- NP	String	CRS + NP, CRS -NP	✓	
Indication of: Eczema	string	yes, no	✓	
Indication of: Allergic Rhinitis	string	yes, no		✓
If diagnosis of osteoporosis	string	yes, no		✓
If diagnosis of type II diabetes	string	yes, no		✓
Start/diagnosis date of osteoporosis	string	string		✓
Start/diagnosis date of type II diabetes	string	string		✓

5.0 Study Outcomes

Objective 2: Potential constructs of natural course of asthma as shown in Table 2.

Table 2 Natural course of asthma constructs

	Type	Value	Description
Remission	Categorical	Yes, No	• No severe exacerbations in the 12 months post biologic initiation date **AND** • LTOCS daily dose of 0 mg use 12 months post biologic initiation, **OR**

			• Asthma control score indicating good control 12 months post biologic initiation date (ACT>19, ACQ <1.5, RCP 0 or 1, aligning with GINA partly or well-controlled categorisation), **OR** • ppFEV1 ≥80%
Clinical outcomes	Discrete	Count (1,2, 3…)	• Exacerbation counts (counts/year)
	Continuous	-	• Total OCS daily dose, mg
	Ordinal	Well controlled Partly controlled Uncontrolled	• Asthma control
	Continuous	-	• Lung function (post-bronchodilator FEV1)
Biomarkers	Continuous	-	• FeNO
	Categorical	<25, ≥25 ppb	
	Continuous	-	• BEC
	Categorical	<300, ≥300 cells/µL	

6.0 Statistical Analysis

Sample Size

The final sample size will depend on the number of individuals with available data meeting inclusion criteria. All patients meeting the eligibility criteria and with sufficient relevant data will be included (i.e. patients will be included in each analysis if they have non-missing data for the variables concerned, irrespective of whether they have non-missing data for all other

variables). Rough feasibility estimates of the numbers of patients with data for the singular clinical outcomes by each proxy (except BACs initiation stage and total OCS) are shown below (CHRONICLE feasibility will be available in the next draft):

Table 3 Feasibility by database (numbers of patients with variables required for proxies)

Timing proxy	Variables	ISAR	OPCRD	CHRONICLE
Age of initiation of Bx	***Age of biologic initiation***			
Duration of asthma from onset	***Age of asthma onset*** + Biologic initiation date + any clinical outcomes (Exacerbation, LTOCS, Control, FEV1)	5302	1,839	
Duration of lung function impairment/ obstruction	***Pre-bx, FEV1*** + ***pre-bx, FVC +*** Biologic initiation date + any clinical outcomes (Exacerbation, LTOCS, Control, FEV1)	5623	1,069	
	Pre-bx, ppFEV1 + Biologic initiation date + any clinical outcomes (Exacerbation, LTOCS, Control, FEV1)	6566	1,178	
Duration of severe asthma[22]	***high or medium pre-bx ICS + LABA start date*** + Biologic initiation date + earliest, any, pre-bx clinical outcomes (Exacerbation, LTOCS, Control, FEV1) + any post-bx clinical outcomes (Exacerbation, LTOCS, Control, FEV1)	2255	1,113 (MD/HD: 915)	
	High pre-bx ICS start date + Biologic initiation date + earliest, any, pre-bx clinical outcomes (Exacerbation, LTOCS, Control, FEV1) + any post-bx clinical outcomes (Exacerbation, LTOCS, Control, FEV1)	1119	1108 (HD: 443)	
Length of time since first requirement of frequent, acute OCS $	***First acute OCS date*** + Biologic initiation date + Exacerbation + LTOCS + Control + FEV1 (all post bx)	n/a	n/a	n/a
	First acute OCS date + Biologic initiation date + any post-bx clinical outcomes (Exacerbation, LTOCS, Control, FEV1)	n/a	n/a	n/a

*TBC as this may be the start date of the current prescription.

Analysis

Objective 1

Descriptive Analysis: Patient characteristics for each of the data sources will be described in tables. The time to initiation of biologic therapy via each proxy will be described using descriptive statistics and graphs as noted below. Distributions at the overall global and country level will be explored to allow for health system and/or data collection differences.

- **Continuous variables** will be summarized as: n (non-missing sample size), mean (or median for skewed and ordinal data) and standard deviation or inter-quartile range (IQR).
- **Categorical variables** will be presented as frequency and percentage (based on the non-missing sample size) or range (if applicable).
- **Graphical presentations** such as dot plots, bar graphs, box plots or histograms will be used to better visualize the distribution of each proxy and inform the statistical approach (e.g. to define exposure categories) used to assess its potential relationship with outcomes in objective 2. Kaplan-Meier curves will be used to compare the profiles of time to biologic initiation between countries for the different proxies of timing.
- Tables will be annotated with the total population size including any missing observations (frequency and %).

To assess the relatedness between proxies, we will apply correlation analyses, pearson correlation analysis (r) or Spearman's rank correlation for highly skewed data, as shown below. All proxies are continuous except BACs initiation stage (ordinal). To clarify, relatedness between proxies will inform the suitability and strength of proxies.

	Duration of asthma	**Duration of lung function impair/obs**	**Duration of severe asthma**	**Duration since freq. acute OCS**	**Total pre-bx OCS**
Duration of asthma	-	-	-		
Duration of lung function impair/obs	r	-	-		
Duration of severe asthma	r	r	-		
Duration since freq. acute OCS	r	r	r		
Total pre-bx OCS	r	r	r	r	
BACs initiation stage	ANOVA	ANOVA	ANOVA	ANOVA	ANOVA

r: Pearson correlation analysis (or Spearman's rank correlation for highly skewed data)

ANOVA: Analysis of variance (or Kruskal-Wallis test for highly skewed data)

Objective 2:

Univariable analyses: Associations between each outcome and proxies of timing of biologic initiation will be assessed via crude analyses as shown in the Table below. If appropriate, the exposure of interest, time to initiation, will be explored both as a continuous and/or a categorical variable ('early/standard' vs 'late') (e.g. to study non-linear associations or to define clinically relevant cut-offs).

* Outcomes at 1 year post biologic initiation or over the first year post biologic initiation

Outcomes	Outcome details	Type	Univariable
Remission		Yes, No	Logistic regression
Clinical outcomes*	Exacerbations	Count	Negative binomial
	Total OCS	Continuous	Linear regression
	Asthma control	Ordinal	Ordinal logistic regression
	Lung function	Continuous	Linear regression
Biomarkers**	FeNO	Continuous	Median change from baseline to 3 months, 12 month, 2 yrs, 3 yrs (Linear or quantile regression)
	BEC	Continuous	

**For biologics that are expected to have effect on the respective biomarker, e.g. Anti-IL5 and BEC.

BACs scores will be analysed at the country level for each biologic class separately (i.e. including only patients whose received that biologic class as their first biologic). BACs score (reflecting the accessibility of a specific biologic class within that country) will be tested for correlation with country level summaries of each of the outcomes. For remission - percentage of patients with remission; asthma control - percentage of patients who were uncontrolled; exacerbations - percentage with >=2 exacerbations; total OCS daily dose - percentage with >10mg per day; FEV_1 - percentage with FEV_1 > 2.0L; FeNO - percentage with ≥25 ppb; BEC - percentage with ≥300 cells/µL.

Selected associations (proxies) from the univariable analyses will be studied further using multivariable regression models. This selection will be made considering the strength and p-

values of the univariable association tests and clinical relevance, with an emphasis on associations which could lead to practice change.

Multivariable Analyses:

Proxies selected from the univariable association tests for timing of biologic initiation and outcomes, will be investigated further using multivariable regression models. The type of model will depend on the nature of the outcome: linear or quantile regression (total OCS, lung function, FeNO, BEC), logistic regression (remission) negative binomial regression (exacerbations), or ordinal logistic regression (asthma control).

The models will be adjusted for factors which have been found to affect biologic effectiveness in other ISAR studies. These include baseline levels of the outcome and potentially confounding factors such as age, smoking status, sex, BMI, comorbidities, medication, and baseline levels of other outcomes such as exacerbations, lung function and asthma control. Where appropriate, country will be included as a random effect in the models to account for differences in disease burden of patients included in the national registries. Interaction terms between factors likely to affect the association will also be included. Completeness of data will also be considered when deciding which factors to include, so that as many patients as possible can be included in the final models and to minimise selection bias in the included patients. Multiple imputation methods or inclusion of “missing” categories may be used to retain clinically important variables in the models if significant proportions of patients have missing data for these variables.

The analyses will include all eligible patients who initiated a biologic and have recorded data on the variables needed for the analysis but sensitivity analyses will also be carried out, stratifying by patients who switched or stopped biologics or had significant interruptions to their treatment. Whilst we will not know the potential effect of the biologics in these patients had they continued, they are of interest because they represent a group who are more likely to have had a poor response to their initial biologic. Stratified analysis will also be carried out to examine differences between countries.

Benralizumab-specific analysis that will address both objectives will be conducted. To clarify, those that initiated biologic therapy using benralizumab will compose the study sample. The timelines listed in section 12 refers to the general analysis using all biologic initiators.

Software

Analysis will be undertaken in Stata or R. Datasets will be received from the data analytics team in either XLS or CSV format, which can be easily imported into the analysis software.

7.0 Limitations

Data Availability and Definition Challenges:

The primary limitation revolves around the variability of the availability and method of data collection across databases and/or countries. Exposure proxies might vary across different clinical settings, which complicates standardising the timing across the study. There is a possibility of selection bias if availability of data is conditional to initiating treatment exceptionally early or exceptionally late.

Another point of variation that may affect this study that we therefore will take into consideration is the differing eligibility criteria and affordability for biologic treatments across countries as well as changing eligibility criteria within a country. Countries with less stringent criteria may exhibit a shorter delay from the time a patient is deemed eligible to when treatment is actually initiated, compared to countries with more complex eligibility requirements. Such key confounders will need carefully assessed and incorporated into the multivariable models, as these variations can significantly influence treatment outcomes.

Natural Course

The key challenge lies in both the quality of pre-biologic initiation (baseline) data and the longitudinal tracking of clinical outcomes and biomarker levels. The integrity of longitudinal data is contingent upon consistent and systematic follow-ups, which may not always be feasible in real-world settings. There may also be discrepancies in how frequently different biomarkers are measured or reported, depending on the clinical protocols of participating sites. This could lead to incomplete data sets for certain key variables such as lung function tests or biomarker assays like FeNO and BEC. While our preliminary data review suggests

comprehensive records for over 3,350 patients*, the completeness and uniformity of these records are critical for robust longitudinal analysis.

*combined OPCRD and ISAR data as of May 2024

General Considerations

This is an exploratory study using real-world observational data so the results will be interpreted as associations and may be subject to biases such as confounding by unobserved factors. Stratified analyses (for groups of special interest) will have smaller sample sizes and may have limited statistical power. The availability of detailed and accurate data on the timing of biologic initiation relative to asthma diagnosis and progression is crucial. Inaccuracies in these timelines could skew the understanding of "early" versus "late" initiation and their respective impacts. Efforts will be made to validate the accuracy (e.g. correlation of proxies, univariate analyses) of the proxies, treatment initiation dates and to ensure that the definitions of early and late initiation are applied in context of country-specific accessibility levels. During interpretation of the data, environmental factors of health system, such as access to phenotyping and affordability, that influence the first biologic prescribed will need incorporated.

8.0 Regulatory and Ethical Compliance

This study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct (EMA 2014; EUPASXXXX#) and with all applicable local and international laws and regulation.

Registration of the ISAR database with the European Union Electronic Register of Post-Authorization studies was also undertaken (ENCEPP/DSPP/23720). ISAR has ethical approval from the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee (ADEPT0218). Governance was provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (registration number: ADEPTXXXX#).

All data collection sites in the International Severe Asthma Registry (ISAR) have obtained regulatory agreement in compliance with specific data transfer laws, country-specific legislation, and relevant ethical boards and organizations.

9.0 Data Dissemination

This is one of the first global RWE studies that we are aware of to investigate the impact of the timing of biologic therapy initiation on disease progression and remission rates in patients with severe asthma. It specifically examines whether early intervention with biologic therapies can alter the course of the disease and improve patient outcomes.

Publications:

The findings will be submitted for publication in peer-reviewed journals that focus on respiratory diseases, biologic therapies, and clinical outcomes.

Conferences:

Results will also be presented at relevant medical and scientific conferences, through abstract presentations and/or discussions.

Authorship:

Authorship will be determined in accordance with the ISAR authorship policy as outline in the ISAR publication charter, which has been approved by the ISAR steering committee. Authorship will recognise significant contributions to the study's conception, analysis, and writing.

10.0 Advisory Group

Professor David Price, Chief Investigator for this 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.

Name	Country / Institution
Ledit R. F. Ardusso	Argentina
María Eugenia Franchi	
Jorge Máspero	
Ardusso Matías	
Ramón Ángel Rojas	
Fernando Saldarini	
Martin Sivori	
Ana María Stok	
Anahi Yañez	
John D. Blakey	Australia
Eve Denton	
Peter G. Gibson	
Mark Hew	
Christine Jenkins	
David Langton	
Peter G. Middleton	
Matthew J. Peters	
Christopher S. Ambrose	AZ
Benjamin Emmanuel	
Cathy Emmas	
Andrew N. Menzies-Gow	
Neda Stjepanovic	
Trung N. Tran	
Hannah Urbanski	
Renaud Louis	Belgium
Florence Schleich	
Paulo Márcio Pitrez	Brazil
George C. Christoff	Bulgaria
Todor A. Popov	
Shawn D. Aaron	Canada

Shelley Abercromby	
Celine Bergeron	
Mohit Bhutani	
Andréanne Côté	
Beth E. Davis	
Delbert R. Dorscheid	
Leiana Hoshyari	
Kenneth R. Chapman	
M. Diane Lougheed	
Leeanne Parris	
Brianne Philipenko	
Mohsen Sadatsafavi	
Hana Serajeddini	
Andrew W. Lindsley	CHRONICLE
Wendy C. Moore	
Reynold A. Panettieri Jr.	
Diana Jimena Cano Rosales	Colombia
Carlos Andrés Celis-Preciado	
Mauricio Durán-Silva	
Maria José Fernández-Sánchez	
Elizabeth Garcia	
Mauricio González-García	
Fabio Bolívar Grimaldos	
Libardo Jiménez-Maldonado	
Julián Esteban Londoño	
Ivan Solarte	
Carlos A. Torres-Duque	
Anne-Sofie Bjerrum	Denmark
Anna von Bülow	
Kjell Erik Julius Håkansson	
Susanne Hansen	
Ole Hilberg	
Celeste M. Porsbjerg	
Linda M. Rasmussen	
Marianne Baastrup Søndergaard	
Charlotte Suppli Ulrik	
Alan Altraja	Estonia

Paula Kauppi	Finland
Lauri Lehtimäki	
Arnaud Bourdin	France
Camille Taillé	
Christian Taube	Germany
Petros Bakakos	Greece
Mina Gaga	
Athena Gogali	
Konstantinos Kostikas	
Stelios Loukides	
Michael P. Makris	
Maria Ntakoula	
Nikolaos G. Papadopoulos	
Andriana I. Papaioannou	
Giannis Paraskevopoulos	
Fotios Psarros	
Zsuzsanna Csoma	Hungary
Dóra Lúdvíksdóttir	Iceland
Sundeep Salvi	India
Richard W. Costello	Ireland
Patrick D. Mitchell	
Giorgio Walter Canonica	Italy
Cristina Cardini	
Giuseppe Guida	
Enrico Heffler	
Takashi Iwanaga	Japan
Hisako Matsumoto	
Tatsuya Nagano	
Tomoko Tajiri	
Mona S. Al-Ahmad	Kuwait
Désirée Larenas-Linnemann	Mexico
Job F.M. Van Boven	Netherlands
James Fingleton	New Zealand
Bernt Bøgvald Aarli	Norway
Sverre Lehmann	
Aaron Beastall	OPC
Lakmini Bulathsinhala	

Victoria Carter	
Nevaashni Eleangovan	
Kirsty Fletton	
Harika Gosala	
Sophie Harriman	
Karen Hosking	
Veronica Mendez Moro	
Chris A. Price	
David B. Price	
Ghislaine Scelo	
Alexander Sterling	
John Townend	
Piotr Kuna	Poland
João A. Fonseca	Portugal
Cláudia Chaves Loureiro	
Graham Lough	REG
Riyad Al-Lehebi	Saudi Arabia
Adeeb A. Bulkhi	
Yahya Habis	
Mariko Siyue Koh	Singapore
Pee Hwee Pang	
Tze Lee Tan	
Mei Fong Liew	
Tunn Ren Tay	
Chin Kook Rhee	South Korea
Borja G. Cosio	Spain
Luis Perez-de-Llano	
Leif Bjermer	Sweden
Pin-Kuei Fu	Taiwan
Horng-Chyuan Lin	
Diahn-Warng Perng	
Chau-Chyun Sheu	
Ming-Ju Tsai	
Bassam Mahboub	United Arab Emirates
Laila Salameh	
John Busby	United Kingdom
Liam G. Heaney	

David J. Jackson	
Pujan H. Patel	
Valeria Perugini	
Paul E. Pfeffer	
Dermot Ryan	
Nicholas Chapman	United States
Flavia Hoyte	
Rohit Katial	
Njira Lugogo	
Diego J. Maselli	
Arjun Mohan	
Kanao Otsu	
Roy Alton Pleasants	
Eileen Wang	
Michael E. Wechsler	

11.0 Research Team

Research Organisation:

Observational & Pragmatic Research Institute (OPRI)

Chief Investigator:

David Price, Professor of Primary Care Respiratory Medicine and OPRI Director

Mobile: +44 7787905057

Office number: +44 2081233923

Skype ID: respiratoryresearch

Email: david@opri.sg

Other Team Members:

General Manager: Victoria Carter [victoria@opri.sg]

Project Lead:

Project Lead:

Project Research Lead:

Data Analyst:

12.0 Project Timeline

Action	Timeline
Protocol finalisation	June 2024
Ethics approval	June 2024
Dataset preparation	July 2024
Analysis & preliminary results	September 2024
Study report	December 2024
Conference abstract	January 2024
Manuscript Draft	February 2025

13.0 References

1. Burnette, A., Wang, Y., Rane, P.B., Chung, Y., Princic, N., Park, J., Llanos, J.P., Lindsley, A.W. and Ambrose, C.S., 2023. Incremental cost burden among patients with severe uncontrolled asthma in the United States. Journal of Managed Care & Specialty Pharmacy, 29(7), pp.825-834.

2. Global Initiative for Asthma, 2022. Global Strategy for Asthma Management and Prevention. Available at: 2022 GINA Main Report - Global Initiative for Asthma - GINA (ginasthma.org) [Accessed 29 April 2024].

3. Ferrari, A.J., Santomauro, D.F., Aali, A., Abate, Y.H., Abbafati, C., Abbastabar, H., Abd ElHafeez, S., Abdelmasseh, M., Abd-Elsalam, S., Abdollahi, A. and Abdullahi, A., 2024. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. The Lancet.

4. Scichilone, N., Barnes, P.J., Battaglia, S., Benfante, A., Brown, R., Canonica, G.W., Caramori, G., Cazzola, M., Centanni, S., Cianferoni, A. and Corsico, A., 2020. The hidden burden of severe asthma: from patient perspective to new opportunities for clinicians. Journal of clinical medicine, 9(8), p.2397.

5. Kardas, G., Panek, M., Kuna, P., Damiański, P. and Kupczyk, M., 2022. Monoclonal antibodies in the management of asthma: Dead ends, current status and future perspectives. Frontiers in Immunology, 13, p.983852.

6. Pfeffer, P.E., Ali, N., Murray, R., Ulrik, C., Tran, T.N., Maspero, J., Peters, M., Christoff, G.C., Sadatsafavi, M., Torres-Duque, C.A. and Altraja, A., 2023. Comparative effectiveness of anti-IL5 and anti-IgE biologic classes in patients with severe asthma eligible for both. Allergy, 78(7), pp.1934-1948.

7. Chen, W., Tran, T.N., Sadatsafavi, M., Murray, R., Wong, N.C.B., Ali, N., Ariti, C., Bulathsinhala, L., Gil, E.G., FitzGerald, J.M. and Alacqua, M., 2023. Impact of initiating biologics in patients with severe asthma on long-term oral corticosteroids or frequent rescue steroids (GLITTER): data from the International Severe Asthma Registry. The Journal of Allergy and Clinical Immunology: In Practice, 11(9), pp.2732-2747.

8. Paoletti, G., Pepys, J., Casini, M., Di Bona, D., Heffler, E., Goh, C.Y., Price, D.B. and Canonica, G.W., 2022. Biologics in severe asthma: the role of real-world evidence from registries. European Respiratory Review, 31(164).

9. McDowell, P.J., McDowell, R., Busby, J., Eastwood, M.C., Patel, P.H., Jackson, D.J., Mansur, A., Patel, M., Burhan, H., Doe, S. and Chaudhuri, R., 2023. Clinical remission in severe asthma with biologic therapy: an analysis from the UK Severe Asthma Registry. European Respiratory Journal, 62(6).

10. Porsbjerg, C.M., Townend, J., Bergeron, C., Christoff, G.C., Katsoulotos, G.P., Larenas-Linnemann, D., Tran, T.N., Al-Lehebi, R., Bosnic-Anticevich, S.Z., Busby, J., Hew, M., Kostikas, K., Papadopoulos, N.G., Pfeffer, P.E., Popov, T.A., Rhee, C.K., Sadatsafavi, M., Tsai, M.-J., Ulrik, C.S., Al-Ahmad, M., Altraja, A., Beastall, A., Bulathsinhala, L., Carter, V., Cosio, B.G., Fletton, K., Hansen, S., Heaney, L.G., Hubbard, R.B., Kuna, P., Murray, R.B., Nagano, T., Pini, L., Cano Rosales, D.J., Schleich, F., Wechsler, M.E., Amaral, R., Bourdin, A., Brusselle, G.G., Chen, W., Chung, L.P., Denton, E., Fonseca, J.A., Hoyte, F., Jackson, D.J., Katial, R., Kirenga, B.J., Koh, M.S., Ławkiedraj, A., Lehtimäki, L., Liew, M.F., Mahboub, B., Martin, N., Menzies-Gow, A.N., Pang, P.H., Papaioannou, A.I., Patel, P.H., Perez-De-Llano, L., Peters, M.J., Ricciardi, L., Rodríguez-Cáceres, B., Solarte, I., Tay, T.R., Torres-Duque, C.A., Wang, E., Zappa, M., Abisheganaden, J., Assing, K.D., Costello, R.W., Gibson, P.G., Heffler, E., Máspero, J., Nicola, S., Perng, D.-W., Puggioni, F., Salvi, S., Sheu, C.-C., Sirena, C., Taillé, C., Tan, T.L., Bjermer, L., Canonica, G.W., Iwanaga, T., Jiménez-Maldonado, L., Taube, C., Brussino, L. and Price, D.B. (2024). Association between pre-biologic T2-biomarker combinations and response to biologics in patients with severe asthma. Frontiers in Immunology. Available at: https://doi.org/10.3389/fimmu.2024.1361891 [Accessed 29 Apr. 2024]

11. Corren, J., Parnes, J.R., Wang, L., Mo, M., Roseti, S.L., Griffiths, J.M. and van der Merwe, R., 2017. Tezepelumab in adults with uncontrolled asthma. New England Journal of Medicine, 377(10), pp.936-946.

12. Ortega, H.G., Liu, M.C., Pavord, I.D., Brusselle, G.G., FitzGerald, J.M., Chetta, A., Humbert, M., Katz, L.E., Keene, O.N., Yancey, S.W. and Chanez, P., 2014. Mepolizumab treatment in patients with severe eosinophilic asthma. New England journal of medicine, 371(13), pp.1198-1207.

13. Porsbjerg, C.M., Menzies-Gow, A.N., Tran, T.N., Murray, R.B., Unni, B., Ang, S.L.A., Alacqua, M., Al-Ahmad, M., Al-Lehebi, R., Altraja, A. and Belevskiy, A.S., 2022. Global variability in administrative approval prescription criteria for biologic therapy in severe asthma. The Journal of Allergy and Clinical Immunology: In Practice, 10(5), pp.1202-1216.

14. Heaney, L.G., de Llano, L.P., Al-Ahmad, M., Backer, V., Busby, J., Canonica, G.W., Christoff, G.C., Cosio, B.G., FitzGerald, J.M., Heffler, E. and Iwanaga, T., 2021. Eosinophilic and noneosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort. Chest, 160(3), pp.814-830

15. Menzies-Gow, A.N., McBrien, C., Unni, B., Porsbjerg, C.M., Al-Ahmad, M., Ambrose, C.S., Dahl Assing, K., von Bülow, A., Busby, J., Cosio, B.G. and FitzGerald, J.M., 2022. Real world biologic use and switch patterns in severe asthma: data from the international severe asthma registry and the US CHRONICLE study. Journal of asthma and allergy, pp.63-78

16. Perez-de-Llano L, Scelo G, Tran TN, Le TT, Faregås M, Cosio BG, Peters M, Pfeffer PE, Al-Ahmad M, Al-Lehebi RO, Altraja A. Exploring Definitions and Predictors of Severe Asthma Clinical Remission Post-Biologic in Adults. American Journal of Respiratory and Critical Care Medicine. 2024 May 3(ja).

17. Ungaro, R.C., Aggarwal, S., Topaloglu, O., Lee, W.J., Clark, R. and Colombel, J.F., 2020. Systematic review and meta-analysis: efficacy and safety of early biologic treatment in adult and paediatric patients with Crohn's disease. Alimentary pharmacology & therapeutics, 51(9), pp.831-842.

18. Mohan A, Panettieri RA, Moore WC, Lugogo NL, Lindsley AW, Carstens DD, Ambrose CS. Greater Exacerbation Reductions With Earlier Biologic Initiation After Severe Asthma Onset: Results From the Chronicle Study. InC102. CLINICAL AND TRANSLATIONAL ADVANCES IN ASTHMA 2024 May (pp. A6699-A6699). American Thoracic Society.

19. Porsbjerg CM, Menzies-Gow AN, Tran TN, et al. Global Variability in Administrative Approval Prescription Criteria for Biologic Therapy in Severe Asthma [published

correction appears in J Allergy Clin Immunol Pract. 2022 Jun;10(6):1673]. *J Allergy Clin Immunol Pract*. 2022;10(5):1202-1216.e23. doi:10.1016/j.jaip.2021.12.027

20. FitzGerald JM, Tran TN, Alacqua M, Altraja A, Backer V, Bjermer L, Bjornsdottir U, Bourdin A, Brusselle G, Bulathsinhala L, Busby J. International severe asthma registry (ISAR): protocol for a global registry. BMC Medical Research Methodology. 2020 Dec;20:1-4

21. Ambrose CS, Chipps BE, Moore WC, Soong W, Trevor J, Ledford DK, Carr WW, Lugogo N, Trudo F, Tran TN, Panettieri RA Jr. The CHRONICLE Study of US Adults with Subspecialist-Treated Severe Asthma: Objectives, Design, and Initial Results. Pragmat Obs Res. 2020 Jul 16;11:77-90. doi: 10.2147/POR.S251120. PMID: 32765156; PMCID: PMC7371434.

22. Mohan, Arjun, et al. Greater Exacerbation Reductions with Earlier Biologic Initiation After Severe Asthma Onset: Results from the CHRONICLE Study. Presented at ATS conference May, 2024.

23. Hansen S, Baastrup Søndergaard M, von Bülow A, Bjerrum AS, Schmid J, Rasmussen LM, Johnsen CR, Ingebrigtsen T, Håkansson KEJ, Johansson SL, Bisgaard M, Assing KD, Hilberg O, Ulrik C, Porsbjerg C. Clinical Response and Remission in Patients With Severe Asthma Treated With Biologic Therapies. Chest. 2024 Feb;165(2):253-266. doi: 10.1016/j.chest.2023.10.046. Epub 2023 Nov 3. PMID: 37925144.

24. Oishi K, Hamada K, Murata Y, Matsuda K, Ohata S, Yamaji Y, Asami-Noyama M, Edakuni N, Kakugawa T, Hirano T, Matsunaga K. A Real-World Study of Achievement Rate and Predictive Factors of Clinical and Deep Remission to Biologics in Patients with Severe Asthma. J Clin Med. 2023 Apr 16;12(8):2900. doi: 10.3390/jcm12082900. PMID: 37109237; PMCID: PMC10142972.

25. Lynam A, Curtis C, Stanley B, Heatley H, Worthington C, Roberts EJ, Price C, Carter V, Dennis J, McGovern A, Price D. Data-Resource Profile: United Kingdom Optimum Patient Care Research Database. Pragmat Obs Res. 2023 Apr 27;14:39-49. doi: 10.2147/POR.S395632. PMID: 37138785; PMCID: PMC10150735.