Study Protocol

# ENLIGHTEN: Assessment of quality improvement in the International Severe Asthma Registry

**Date:**
10 Feb 2025

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 Director

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

**Study Sponsor:**

OPRI UK

**Primary Contact:**

Name: Freya.Tyrer@opri.sg

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|---|---|
| **TITLE** | **ENLIGHTEN: Assessment of quality improvement in the International Severe Asthma Registry** |
| Subtitle | |
| Protocol version number | V3.0 |
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| Product code | Not applicable |
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| Marketing authorisation number | Not applicable |
| Study aims and objectives | The aim of this study is to evaluate the quality of the International Severe Asthma Register (ISAR) data over time and during quality initiatives by investigating changes in process measures (completeness of key research data) and clinical measures (long-term oral corticosteroid [LTOCS] prescribing and initiation of biologics). Specific objectives are:<br><br>1. To investigate the proportion of patients in ISAR with 90% and 100% completeness of key research variables (as voted on in a 2023/24 Delphi exercise) from 1 May 2017 to the latest date available.<br>2. To investigate completeness of recording of all core variables in ISAR (as voted during the 2024 Delphi exercise).<br>3. To investigate how:<br>a. the proportion of patients in ISAR who are prescribed LTOCS vary over time<br>b. the proportion of patients on LTOCS that are stopped/reduced vary over time.<br>4. To investigate initiation to biologic treatments by severity of asthma indicators over time. |
| Countries of study | All countries/sites contributing to the ISAR initiative who have consented for their data to be used in research |
| Author(s) | Freya Tyrer, Lakmini Bulathsinhala, Ghislaine Scelo, John Townend, Veronica Mendez, Victoria Carter, David Price |

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## List Of Abbreviations

| Abbreviation or special term | Explanation |
|---|---|
| ADEPT | Anonymised Data Ethics & Protocol Transparency |
| ISAR | International Severe Asthma Registry |
| IgE | Immunoglobin E |
| IL-4 | Interleukin-4 |
| IL-5 | Interleukin-5 |
| ISC | ISAR Steering Committee |
| KPR | Key prior reviews (i.e. first patient visit on the ISAR database or where patients starts/switches a biologic) |
| LTOCS | Long-term oral corticosteroids |
| LTRA | Leukotrine Receptor Antagonist |
| OPC | Optimum Patient Care |
| OPRI | Observational and Pragmatic Research Institute |
| RR | Re-review (follow-up visits on the ISAR that do not meet the criteria for a KPR) |
| TSLP | Thymic Stromal Lymphopoietin |

## 1. Background

Quality improvement (QI) within the healthcare setting is a broad term that describes improved patient experiences and outcomes achieved through a systematic change method and strategies (1). These improvements extend to electronic health records as data are increasingly used to decide whether high-quality care is being provided to patients, often through an investigation of both process (e.g. data accuracy and completeness) and clinical outcomes (e.g. better control of symptoms) (2).

Healthcare registry data require robust quality improvement initiatives as they have the potential to provide a rich source of surveillance data on healthcare patterns, clinical decision making and delivery of interventions that can, ultimately, improve patient outcomes (3). However, registry data also rely heavily on understanding how the data were derived and why they were recorded so that its users can interpret the results meaningfully. For example, when using registry data that combine information on patients from different sites and countries, consideration needs to be made of relevant healthcare systems and specific national policy initiatives.

This study investigates the quality of the International Severe Asthma Register (ISAR) data over time and during key policy and quality improvement initiatives of a longitudinal, real-life data registry for patients with severe asthma (4). The ISAR provides a useful framework through which other quality improvement initiatives can be developed as it is underpinned by data quality goals that align with stakeholder needs and the needs of patients with severe asthma. Such goals include high level of completeness in the collection of core variables and key research variables, which help to inform both day-to-day clinical decision-making (e.g. by identifying patients, who may benefit from further monitoring or treatment), and promote severe asthma research (e.g. treatment efficacy/effectiveness). At the forefront of the ISAR initiative's original (and continuing) mission was to reduce long-term oral corticosteroid (LTOCS) exposure (5) and facilitate the provision of an international consortium for research collaboration in respiratory medicine and patient care (6). A minimum core set of variables for the ISAR was developed in 2017 as part of a modified Delphi process consisting of 3 iterative rounds and two face-to-face meetings with a panel of 27 international experts in the field of severe asthma research (7). A follow-on Delphi exercise was conducted in 2023 to identify key variables for use in research, which was further refined in 2024. Additional quality improvement plans for the ISAR were introduced from 2023. These included the introduction of a data quality report, a country-specific data quality dashboard, face-to-face meetings on

data quality issues, and (optional for some countries) an optimised electronic case report form (eCRF).

# 2. Study Aims and Objectives

## 2.1. Study Aims

ENLIGHTEN aims to explore the quality of ISAR data over time and during key policy and improvement change initiatives by investigating changes in process measures (completeness of key research data) and clinical practice (severity indicators of biologic initiation) and outcomes (long-term oral corticosteroid [LTOCS] prescribing). Although based on ISAR's quality improvement implementation plan and target goals for each country, it forms a distinct research exercise to look more broadly at the impact of the ISAR collaboration on data quality and patient care. The findings will be presented in aggregated form, stratified by country, where appropriate.

The aim of the ENLIGHTEN project is to investigate the quality of the International Severe Asthma Register (ISAR) data over time and during key practice change initiatives in relation to completeness of key research data and patient outcomes. As well as data quality, we also aim to investigate how data has changed on ISAR in terms of changes in clinical practice.

## 2.2. Study Objectives

**PROCESS OUTCOMES**

**Objective 1**: To investigate the proportion of patients on the ISAR with 90% and 100% completeness of key research variables (as voted on in a 2023/24 Delphi exercise – see **Section 5.0; Table 1**) from 1 May 2017 to the latest data available.
**Objective 2:** To investigate completeness of recording of all core variables in ISAR (as voted during the 2024 Delphi exercise).

**CLINICAL PRACTICE**

**Objective 3**: To investigate how: (i) the proportion of patients on the ISAR who are prescribed LTOCS vary over time; and (ii) the proportion of patients on LTOCS that are stopped/reduced vary over time.

**Objective 4**: To investigate initiation to biologic treatments by severity of asthma indicators over time.

# 3. Study Design

This study follows a prospective cohort design. As sites and countries that contribute to the ISAR have retrospectively corrected variables in response to queries and data quality requirements, we will use a repeated cross-sectional design as well as historical snapshot data to investigate contemporaneous relationships between core variables (for objectives 1 and 2). For clinical outcomes (objectives 3 and 4), we will investigate how clinical practice has changed over time.

As well as considering individual countries, we will take account (through modelling) of when the country commenced participation in the ISAR (including contract arrangements and source of financing), different data provision procedures at participating countries (e.g. through the RedCap electronic data system or other bespoke methods),and whether the visit was for a new patient (key prior review [KPR] - new patient) or a follow-up visit (re-review [RR]).

# 4. Study Population

## 4.1. Data Sources

This study uses data on eligible patients contributing to the ISAR programme from those countries that have consented for their data to be used for research.

## 4.2. Inclusion and Exclusion Criteria

**Inclusion Criteria**

- Patient meets criteria for severe asthma:
  - On Global Initiative for Asthma (GINA 2021) Step 5 (8)
  - Uncontrolled on GINA Step 4, at least one of the following:

- poor symptom control: asthma control questionnaire ACQ>1.5, ACT<20 or “not well controlled" by National Education and Prevention Program [NAEPP]/GINA guidelines (8,9)
- airflow limitation: after appropriate bronchodilator withhold Forced expiratory volume in one second (FEV1) <80% predicted (in the face of reduced FEV1/forced vital capacity [FVC] defined as less than the lower limit of normal)
- serious exacerbations: at least one hospitalisation, intensive care unit (ICU) stay or mechanical ventilation in the previous year
- frequent exacerbations: two or more bursts of systemic corticosteroids (>3 days each) in the previous year

**Exclusion Criteria**

- For Objective (3), patients will be excluded if they have an unknown LTOCS status (objective 3 – although we will look at ‘unknown’ LTOCS that has been completed retrospectively to assess any potential for bias), if they have information on only 1 visit, and/or they are not taking LTOCS at their baseline visit (defined by first visit with LTOCS=yes). For Objective (4), patients will be excluded if they have unknown biologic status and/or none of the asthma severity indicators at baseline (defined by first visit with asthma severity indicator=yes)
- Patients (from some countries/regions) who have not consented for their data to be used for research purposes and/or data that have been approved for specific studies only.

## 5. Study Variables and Study Outcome Definitions

### Objective 1: Proportion of patients on the ISAR with 100% completeness of key research variables from 2017 to latest date available

**Outcome:** Proportion of patients meeting 100% completeness of key research variables by patient status (i.e. new patients and follow-up visits)
**Exposure:** Time (calendar year and pre-specified periods of change)
**Covariates:** Country (numbers allowing), Country-specific factors (method of data provision, healthcare setting, date of participating in ISAR), visit-specific factors

We will focus on key research variables, as voted for in the 2023/24 Delphi exercise. For first visits or where patient starts or switches a biologic (**KPR visits**), 16 variables will be investigated (see **Table 1**). For **re-review (RR)** visits, 11 variables will be investigated.

We will divide the visit dates into calendar years and assess the proportion of all individuals meeting the criteria for 90% and 100% key research variables to assess whether there are any changes/trends over time. We will also investigate before and after completeness over key periods (e.g. introduction of quality improvement initiatives [period from introduction of data quality [DQ] dashboards, reports and face-to-face meetings], changes in data capture systems) where we might expect completeness to change. As well as looking at changes by calendar year for the most recent complete data set, we will use snapshot data to assess completeness and accuracy of data in different snapshot periods. This process will allow for the evaluation of backdated quality improvements in the data. For example, 2021 data from 2024 will be compared with 2021 data captured in 2021, 2022 and 2023 (and different quarters within this period where we might expect to see changes).

**Table 1. Key research variables as voted for in Delphi by key prior review (KPR) and re-review (RR) visits**

| KEY | KPR & RR | KPR ONLY | RR ONLY |
|---|---|---|---|

| Category | Variable Field Name | Key prior review | Re-review |
|---|---|---|---|
| **DOV** | Date of visit | ☑ | ☑ |
| **AGE, GENDER, HEIGHT & WEIGHT** | Date of Birth | ☑ | ☒ |
| | Gender | | |
| | Weight | | |
| | Height | | |
| **SMOKING STATUS** | What is the current smoking status of the patient? | ☑ | ☑ |
| **ASTHMA ONSET** | At what age did the patient's asthma symptoms begin? Whole years or months if < 1year | ☑ | ☒ |
| **EXACERBATION** | Number of exacerbations requiring rescue (systemic/oral) steroids in the past 12 months? | ☑ | ☑ |
| **HOSPITAL ADMISSION** | Total number of hospital admissions for asthma in the past 12 months? | ☑ | ☑ |
| **CHRONIC RHINOSINUSITUS** | Indication of: Chronic Rhinosinusitis | ☑ | ☒ |

| | | | |
|---|---|---|---|
| **NASAL POLYPS** | Indication of: Nasal Polyps | ☑ | ☒ |
| **HIGHEST BLOOD OESINOPHIL COUNT** | What is the Highest Blood Eosinophil Count (within the past year)? **Also built from blood oesonophil records if missing** | ☑ | ☒ |
| **IGE COUNT** | What is the IgE Count (latest) | ☑ | ☒ |
| **POST-BD-FEV1 or ON TREATMENT FEV1** | Post-bronchodilator FEV1 | ☑ | ☑ |
| **ASTHMA CONTROL** | Asthma (symptom) Control | ☑ | ☑ |
| **LTOCS AND DAILY DOSE** | Is the patient prescribed Maintenance Oral Steroids? | ☑ | ☑ |
| | Daily dose of Maintenance Oral Steroids | | |
| **PRESCRIPTION ICS+LABA/ICS/LABA/LAMA/THEO/LTRA** | Is the patient on a prescription for ICS+LABA combination therapy? | ☑ | ☑ |
| | Is the patient on a prescription for ICS (only)? | | |
| | Is the patient on a prescription for LABA (only)? | | |
| | Is the patient on a prescription for LAMA? | | |
| | Is the patient on a prescription for Theophyllines? | | |
| | Is the patient on a prescription for Leukotrine Receptor Antagonist (LTRA)? | | |
| | Is the patient on a prescription for Macrolide Antibiotic Treatment? | | |
| **BIOLOGIC** | Prescription for Anti-Interleukin 4 (Anti-IL4) Treatment? | ☑ | ☑ |
| | Prescription for Anti-Interleukin 5 (Anti-IL5) Treatment? | | |
| | Prescription for Anti-IgE Treatment? | | |
| | Prescription for Anti-TSLP Treatment? | | |
| **BIOLOGIC START DATE** | Start Date of Anti-Interleukin 4 (Anti-IL4) Treatment? | ☑ | ☑ |
| | Start Date of Anti-Interleukin 5 (Anti-IL5) Treatment? | | |
| | Start Date of Anti-IgE Treatment? | | |
| | Start Date of Anti-TSLP Treatment | | |
| **REASON FOR SWITCH** | Reason for biologic switch | ☒ | ☑ |

## Objective 2: Completeness of recording of core variables in ISAR over time

**Outcome:** Proportion of core variables that are complete for each patient

**Exposure:** Time (calendar year and pre-specified periods of change)

**Covariates:** Age, gender, country, country-specific factors, visit-specific factors

We will investigate the percentage of patients with 90% complete core variables in ISAR over time. The completeness of individual core variables will also be investigated, as well as

the proportion of individuals that meet criteria for ≥90% completeness of core variables. There are 38 core variables in the ISAR, as voted for in the Delphi 2017 exercise. These are shown in **Appendix 1** (Section 13.1) along with some more information about the ISAR schedules. We will also investigate patient characteristics associated with completeness of data for targeted strategies.

### Objective 3: Differential characteristics and proportion of patients on LTOCS in the ISAR registry over time

**Outcome:** Proportion of patients on LTOCS (at visit)
**Exposure:** Time (calendar year and pre-specified periods of change)
**Covariates:** Age, gender, country, country-specific factors

The characteristics of patients in the ISAR registry who are prescribed LTOCS are likely to change with policy initiatives, awareness of serious adverse events, increased knowledge about asthma among participating sites, and biologic availability. ISAR may also have prompted behaviour change among clinicians who treat patients with severe asthma thereby affecting their treatments and/or outcomes. We will assess trends in LTOCS use over time, adjusting for age and gender, and stratifying by country and country-specific factors (e.g. participation in ISAR consortium, data capture system). We will also evaluate proportion and time to stopping/reducing the dose (≤5mg) of LTOCS to assess differences in clinical practice over calendar time.

### Objective 4: Severity of asthma in those initiating biologic treatment over time

**Outcome:** Initiation of biologic treatment by asthma severity indicator
**Exposure:** Time (calendar year and pre-specified periods of change)
**Covariates:** Age, gender, country-specific factors

We will investigate and describe initiation of first biologic treatment by asthma severity indicator over calendar time, also adjusted for age and gender. We will further explore whether this changes as quality of data improves and/or in response to key practice change initiatives (quality improvement, seminal papers). Asthma severity indicators will be defined using each of the following criteria: LTOCS use; pre-visit exacerbation(s); asthma control status; and lung function [FEV1% predicted] (12).

# 6. Statistical Analysis

## 6.1. Sample Size

A feasibility count conducted in November 2024 identified 96,125 visits with information in ISAR from May 2017. Of these, the provision of data to the central site was through the ISAR electronic data case report form for 81,396 (85%) patients, whereas data on 20,293 (15%) patients was sent through bespoke methods. Around one quarter of visits were KPR (either new patients or switches/new biologic treatments) and three-quarters were RR (follow-up visits).

| ISAR feasibility count: 26 November 2024 | | | |
|---|---|---|---|
| **Total number of patients** | | 96,125 | 100% |
| **Data transfer method** | Bespoke | 14,728 | 15% |
| | Electronic data capture | 81,397 | 85% |
| **Visit type** | New patient visits | 20,293 | 21% |
| | Switch/New biologic | 3,036 | 3% |
| | Re-review | 72,796 | 76% |

## 6.2. Software

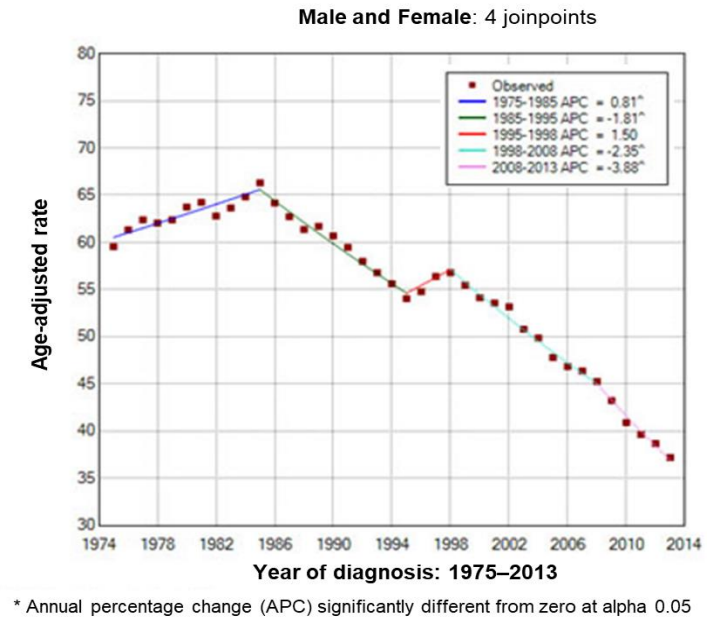
This project will use Stata statistical software v15.1 (10), SQL Server Management Studio (v20) and joinpoint trend analysis software from the Surveillance Research Program Cancer Institute Version 5.30 (Division of Cancer Control & Population Sciences, National Cancer Institute, US): https://surveillance.cancer.gov/joinpoint/ (11).

## 6.3. Statistical methods for each objective

For all objectives (apart from objective 4), trends in reporting (both longitudinally and using repeated cross-sectional analyses using historical data snapshots) will be partially investigated using joinpoint analysis. Joinpoint regression is a piecewise linear (or log-linear) regression to describe trends, changes in trends and specific change-points (or joinpoints) in relation to the characteristics of disease or another outcome over time. The joinpoint trend analysis software used starts with the minimum number of joinpoints (i.e. zero joinpoints – a straight line) and tests whether more joinpoints are statistically significant and need to be

added to the model. Up to three joinpoints will be investigated using a weighted Bayesian Information Criterion (BIC) test (recommended by the Joinpoint software for its optimal performance and sensitivity to small changes in trends) (13,14) and a parametric method. A significant difference from no change of each segment will be evaluated using a 5% level of probability ($p<0.05$) using annual percentage changes (APC) to indicate fluctuations in trends across distinct intervals (14). See **Figure 1** for a sample joinpoint graph adapted from the graph shown on the National Cancer Institute website: https://surveillance.cancer.gov/joinpoint/.

**Figure 1: Sample joinpoint analysis graph, showing 4 joinpoints**




* Source: https://surveillance.cancer.gov/joinpoint/

The software used for the trend analyses identifies inflections in the data without pre-specified knowledge at which the time points are expected to occur. In some situations, this knowledge is important as we may wish to investigate whether improvements have occurred after the introduction of specific interventions, such as new data capture systems and/or change in response to latest research evidence, policy initiatives and QI initiatives. We also wish to evaluate whether the quality improvement plans for the ISAR introduced from 2023 (data quality report, country-specific data quality dashboard, face-to-face meetings on data quality

issues) had any impact on data quality. We will also explore the effects of the confounder COVID and adjust for this, if necessary. Therefore, we will investigate how trends differ before and after a given intervention using a single group interrupted time series analysis (ITSA) using calendar year as the time variable. This will involve creating a spline of year with a knot placed at either one or several intervention periods and creating a variable to partition time periods to before and after the given intervention. Where the key period differs for each country (e.g. introduction of QI initiatives as part of the ISAR), we will explore changes either side of the key period (set to be time zero). A linear mixed effects model will be used to assess the percentage of variables that are complete (objective 2) by intervention period and covariates, modelling variation in country as a random effect. The odds of LTOC use (objective 3) pre- and post-intervention period will use a logistic mixed effects model, also using a random intercept for each country. For both methods, 95% confidence intervals will be calculated using bootstrapping techniques. For the time-to-event components of objective 3 (i.e. time from LTOCS to stopping/reducing LTOCS) and objective 4 (i.e. time to initiating biologic by asthma severity indicator), we will use time-to-event analyses (both non-parametric and flexible parametric methods).

**Objective 1**: **Proportion of patients in ISAR with 100% completeness of key research variables from 1 May 2017 to latest date available**

We will use data from the ISAR registry from May 2017 to the latest date available to calculate the proportion of patients in each calendar year with 100% completeness of key research variables from 1 May 2017 to latest data available. Reviews will be stratified into KPRs and RRs, and method of provision for each country (i.e. ISAR-built electronic data capture vs bespoke). Joinpoint analysis will be used to identify each calendar year period (i.e. the predictor variable) at which there is a change in the proportion of patients reaching 100% completeness and the size of this change (percentage change in rate per calendar year). A log-linear model will be used to analyse percentage change in rate over time, reporting on the linear trend in each segment, also stratifying by country to explore country-specific effects. We will also investigate specific inflection points/periods during the observation period using ITSA.

**Objective 2**: **Completeness of recording of all core variables in ISAR**

Annual trends and changes in the proportion of core variables will be investigated in ISAR, also stratifying by country and provision of data method. The completeness of individual core variables will also be investigated to assess the variables that are least likely to be complete.

We will use a combination of joinpoint regression (to investigate trends) and ITSA (to investigate pre-specified inflection time points) with variation in country modelled as a random effect for this component of the analysis, also stratifying by data capture method. **Appendix 1** (Section 13.1) shows the complete list of core variables in ISAR.

**Objective 3: Differences in the proportion of patients in ISAR who are prescribed LTOCS varies over time, and the characteristics of these patients**

Trends in the proportion of patients with a LTOCS prescription in a given year (i.e. yes/no) and average dose of LTOCS will be described and plotted by calendar year using a combination of joinpoint regression and ITSA to analyse significant changes in trends, also stratifying by country-specific data capture method. For those on LTOCS, we will also investigate the probability of stopping/reducing LTOCS dose (<5mg) using time-to-event analysis (non-parametric [Kaplan-Meier] and flexible parametric methods). Patient characteristics for people with and without missing/incomplete data on LTOCS will also be compared.

**Objective 4: Trends in the severity of asthma indicators in those initiating biologic treatment over time**

The probability of initiating biologic treatments by asthma severity indicator and calendar year will be investigated using time-to-event analyses (non-parametric and flexible parametric models).

## 7. 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 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 from sites is de-identified in the form of anonymised patient IDs. The data will be retrieved by Optimal Patient Care/Observational & Pragmatic Research Institute 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. Data Dissemination

This study is the first of its kind to formally investigate data quality improvements over time in ISAR. The assessment of clinical outcomes (objectives 2 and 3) over time will help to assure both data quality and patient outcomes.

**Publications:**

The findings will be submitted for publication in peer-reviewed journals that focus on data quality (Data, JAMIA Open; Objective 1) and respiratory diseases, biologic therapies, and clinical outcomes (Objectives 2 and 3).

**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.

## 9. Project management group and wider steering committee group

Professor David Price, Chief Investigator for the study, is the chair of the ISAR Steering Committee (ISC).

The project management group for this project will be led by Professor David Price. Other members of the project management group are listed below.

| No | Name | Country / Institution |
|---|---|---|
| 1 | Melina Girbal | Argentina |
| 2 | Jorge Máspero | Argentina |
| 3 | Fernando Saldarini | Argentina |
| 4 | Anahí Yañez | Argentina |
| 5 | Cathy Emmas | AstraZeneca |
| 6 | Hisham Farouk | AstraZeneca |
| 7 | Robert Fogel | AstraZeneca |
| 8 | Andrew N. Menzies-Gow | AstraZeneca |
| 9 | Neda Stjepanovic | AstraZeneca |
| 10 | Trung N. Tran | AstraZeneca |
| 11 | Hannah Urbanski | AstraZeneca |
| 12 | Mark Hew | Australia |
| 13 | Anne Chèvremont | Belgium |
| 14 | Renaud Louis | Belgium |
| 15 | Florence Schleich | Belgium |
| 16 | Marcos Antunes Brum | Brazil |
| 17 | Paulo Márcio Pitrez | Brazil |
| 18 | George C. Christoff | Bulgaria |
| 19 | Todor A. Popov | Bulgaria |
| 20 | Shelley Abercromby | Canada |
| 21 | Celine Bergeron | Canada |
| 22 | Kenneth R. Chapman | Canada |
| 23 | Andréanne Côté | Canada |
| 24 | Delbert R. Dorscheid | Canada |
| 25 | Mohsen Sadatsafavi | Canada |
| 26 | Maria José Fernández-Sánchez | Colombia |
| 27 | Patricia Parada-Tovar | Colombia |
| 28 | Isabella Perna Reyes | Colombia |
| 29 | Carlos A. Torres-Duque | Colombia |
| 30 | Kjell Erik Julius Håkansson | Denmark |
| 31 | Susanne Hansen | Denmark |
| 32 | Celeste M. Porsbjerg | Denmark |
| 33 | Marianne Baastrup Søndergaard | Denmark |
| 34 | Charlotte Suppli Ulrik | Denmark |
| 35 | Juan Carlos Calderon | Ecuador |
| 36 | Ivan Cherrez-Ojeda | Ecuador |
| 37 | Karla Robles | Ecuador |
| 38 | Alan Altraja | Estonia |
| 39 | Kai Kliiman | Estonia |
| 40 | Arnaud Bourdin | France |
| 41 | Camille Taillé | France |
| 42 | Christian Taube | Germany |
| 43 | Konstantinos P. Exarchos | Greece |

**Commented [PL1]:** @Freya Tyrer please note I have removed the AU collaborators and updated the list in tracked changes. Feel free to accept if all in order. Thank you.

| | | |
|---|---|---|
| 44 | Maria Kallieri | Greece |
| 45 | Konstantinos Kostikas | Greece |
| 46 | Nikolaos G. Papadopoulos | Greece |
| 47 | Andriana I. Papaioannou | Greece |
| 48 | Sundeep Salvi | India |
| 49 | Richard W. Costello | Ireland |
| 50 | Patrick D. Mitchell | Ireland |
| 51 | Caoimhe Murphy | Ireland Tallaght |
| 52 | Giorgio Walter Canonica | Italy |
| 53 | Cristina Cardini | Italy |
| 54 | Enrico Heffler | Italy |
| 55 | Concetta Sirena | Italy |
| 56 | Takashi Iwanaga | Japan |
| 57 | Mona S. Al-Ahmad | Kuwait |
| 58 | Sumi Rajeevan | Kuwait |
| 59 | Désirée Larenas-Linnemann | Mexico |
| 60 | Bernt Bøgvald Aarli | Norway |
| 61 | Sverre Lehmann | Norway |
| 62 | Piotr Kuna | Poland |
| 63 | Ana Alves da Silva | Portugal |
| 64 | Hadassa Santos | Portugal |
| 65 | Graham Lough | REG |
| 66 | Riyad Al-Lehebi | Saudi Arabia |
| 67 | Wenjia Chen | Singapore |
| 68 | Tavleen Kaur Jaggi | Singapore |
| 69 | Mariko Siyue Koh | Singapore |
| 70 | Esther Ann | South korea |
| 71 | Chin Kook Rhee | South Korea |
| 72 | Borja G. Cosio | Spain |
| 73 | Luis Perez-de-Llano | Spain |
| 74 | Hsin-Kuo Bruce Ko | Taiwan |
| 75 | Diahn-Warng Perng | Taiwan |
| 76 | Ming-Ju Tsai | Taiwan |
| 77 | Bassam Mahboub | United Arab Emirates |
| 78 | Laila Salameh | United Arab Emirates |
| 79 | John Busby | United Kingdom |
| 80 | Liam G. Heaney | United Kingdom |
| 81 | David J. Jackson | United Kingdom |
| 82 | Pujan H. Patel | United Kingdom |
| 83 | Paul E. Pfeffer | United Kingdom |
| 84 | Dermot Ryan | United Kingdom |
| 85 | Flavia Hoyte | United States |
| 86 | Rohit Katial | United States |
| 87 | Njira Lugogo | United States |

| | | |
|---|---|---|
| 88 | Roy Alton Pleasants | United States |
| 89 | Eileen Wang | United States |
| 90 | Michael E. Wechsler | United States |
| 91 | Lakmini Bulathsinhala | OPC |
| 92 | Victoria Carter | OPC |
| 93 | Ghislaine Scelo | OPC |
| 94 | John Townend | OPC |
| 95 | Freya Tyrer | OPC |
| 96 | David B. Price | OPC |

## 10. 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 OPRI/OPC Team Members:**

Research & Operations Director: Victoria Carter [victoria@opri.sg]
Project Research Lead: Freya Tyrer [Freya.Tyrer@opri.sg]
Research support: Ghislaine Scelo [Ghislaine.Scelo@opri.sg], Lakmini Bulathsinhala, Veronica Mendez
Data Analyst: Aaron Beastall
Statistician: John Townend

## 11. Timelines

| Action | Timeline |
|---|---|
| Contract signature | March 2025 |
| Literature search & proposal | November 2024 |
| Proposal sign-off internally | January 2025 |
| Protocol delivery to steering group | January 2025 |
| Protocol sign-off | February 2025 |

| | |
|---|---|
| Dataset delivery + ADEPT approval | February 2025 |
| Analyses | February 2025 |
| REG presentation | March 2025 |
| Final study report | August 2025 |
| Study report sign-off | September 2025 |
| Manuscript | October 2025 |

## 12. References

1. Øvreitveit J. Does improving quality save Money? A Review of the evidence of which improvements to quality reduce costs to health service providers. London; 2009.
2. Langley GJ, Moen RD, Nolan KM. The improvement guide. 2nd ed. San Francisco, CA: Jossey-Bas; 2009.
3. Gliklich R., Leavy M, Dreyer N. Chapter 13, Analysis, interpretation, and reporting of registry data to evaluate outcomes. In: Gliklich RE, Leavy MB, Dreyer NA, editors. Registries for Evaluating Patient Outcomes: A User's Guide [Internet: https://www.ncbi.nlm.nih.gov/books/NBK562558/]]. 4th ed. Rockville, MD: Agency for Healthcare Research and Quality (US); 2020.
4. FitzGerald JM, Tran TN, Alacqua M, Altraja A, Backer V, Bjermer L, et al. International severe asthma registry (ISAR): protocol for a global registry. BMC Med Res Methodol. 2020 Dec 14;20(1):212.
5. Chen W, Tran TN, Sadatsafavi M, Murray R, Wong NCB, Ali N, et al. 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. J Allergy Clin Immunol Pract. 2023 Sep;11(9):2732–47.
6. ISAR Study Group. International Severe Asthma Registry: Mission Statement. Chest. 2020;157(4):805-814.
7. Bulathsinhala L, Eleangovan N, Heaney LG, et al. Development of the International Severe Asthma Registry (ISAR): A Modified Delphi Study [published correction appears in J Allergy Clin Immunol Pract. 2021 Nov;9(11):4182. doi: 10.1016/j.jaip.2021.09.004]. J Allergy Clin Immunol Pract. 2019;7(2):578-588.e2.
8. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated 2021. Accessed Dec 22, 2024. https://ginasthma.org/ wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf
9. Cloutier MM, Baptist AP, Blake KV et al. Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Journal of Allergy and Clinical Immunology 2020. 146(6):1217-1270.
10. Stata Statistical Software: Release 15.1. StataCorp. College Station,TX; 2017.
11. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates [published correction appears in Stat Med 2001 Feb 28;20(4):655]. Stat Med. 2000;19(3):335-351.

12. Lommatzsch M, Buhl R, Canonica GW, Ribas CD, Nagase H, Brusselle GG, et al. Pioneering a paradigm shift in asthma management: remission as a treatment goal. Lancet Respir Med. 2024; 12:96–99.
13. Schwarz G., Estimating the dimension of a model, Ann. Stat. 6 (1978), pp. 461–464.
14. Li Huizhang D. Application of Joinpoint regression model in cancer epidemiological time trend analysis. Chin J Prev Med. 2020;54:908–12.

# 13. Appendices

## 13.1. Appendix 1: Core variables in ISAR

The contract with each of the study countries and sites who contribute to the ISAR collaborative incorporates four schedules of data collection. Schedule 2 is the list of core variables, required at every visit. Schedule 4 contains a list of key research variables for key prior reviews, which incorporate first visits and those where a patient starts or switches biologic therapies. Schedule 5 is the list of key research variables for re-reviews (follow-up visits) and contains substantially fewer variables than the key prior reviews. Finally, schedule 6 contains variables for any information on key prior reviews before 2023 and does not include spirometry as this was introduced as a key variable in the 2023 Delphi exercise (including collaborators across each site/country). Information on baseline FeNO measurements was also included as a key research variable at baseline (i.e. key prior review) in the 2023 Delphi exercise. It was later dropped in a subsequent 2024 Delphi exercise.

All variables collected for the ISAR initiative, the schedule to which they contribute, and whether they are included as a core variable or as a key research variable at the ISAR patients' key prior review or re-review are shown in **Table A1**.

**Table A1: All core variables collected for ISAR initiative, their inclusion in each data collection schedule, and their contribution to patients' key prior review and/or re-review as a a key research variable**

| KEY VARIABLE STATUS | |
|---|---|
| | Both KPR and RR |
| | KPR only |
| | RR only |

| | Core variable only |
|---|---|

| Category | Variable Field Name | Core variable | Key variable (KPR) | Key variable (RR) | Key/core variable by schedule number | | | |
|---|---|---|---|---|---|---|---|---|
| **Number of variables** | | | | | **2** | **4** | **5** | **6** |
| **DOV** | Date of visit | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ |
| **AGE, GENDER, HEIGHT & WEIGHT** | Date of Birth | ☑ | ☑ | ☒ | ☑ | ☑ | ☒ | ☑ |
| | Gender | | | | | | | |
| | Weight | | | | | | | |
| | Height | | | | | | | |
| **ETHNICITY** | Ethnicity | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **OCCUPATION** | What is the current occupation of the patient? | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **SMOKING STATUS** | What is the current smoking status of the patient? | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ |
| **ASTHMA ONSET** | At what age did the patient's asthma symptoms begin? Whole years or months if < 1year | ☑ | ☑ | ☒ | ☑ | ☑ | ☒ | ☑ |
| **OTHER FACTORS** | Are there any <u>other</u> factors contributing to severe asthma symptoms? | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **EXACERBATION** | Number of exacerbations requiring rescue steroids in the past 12 months? | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ |
| **INVASIVE VENTILATIONS** | Total number of episodes of invasive ventilation ever? | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **EMERG** | Total number of A&E attendances for asthma in the past 12 months? | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **HOSPITAL ADMISSION** | Total number of hospital admissions for asthma in the past 12 months? | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ |
| **ECZEMA** | Indication of: Eczema | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **ALLERGIC RHINITIS** | Indication of: Allergic Rhinitis | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **CHRONIC RHINOSINUSITUS** | Indication of: Chronic Rhinosinusitis | ☑ | ☑ | ☒ | ☑ | ☑ | ☒ | ☑ |
| **NASAL POLYPS** | Indication of: Nasal Polyps | ☑ | ☑ | ☒ | ☑ | ☑ | ☒ | ☑ |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **OSTEOP** | Does the patient have a diagnosis of Osteoporosis? | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **OSTEOP_DTE** | Diagnosis date for Osteoporosis | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **T2DIAB** | Does the patient have a diagnosis of Type II Diabetes | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **T2DIAB_DTE** | Diagnosis date for Type II Diabetes | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **HIGHEST BLOOD OESINOPHIL COUNT** | What is the Highest Blood Eosinophil Count (within the past year)? | ☑ | ☑ | ☒ | ☑ | ☑ | ☒ | ☑ |
| **BEOS_DTE** | Date of highest blood Eosinophil count (within the past year) | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **BEOS_CNT** | What is the Current Blood Eosinophil Count (latest)? | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **IGE COUNT** | What is the IgE Count (latest) | ☑ | ☑ | ☒ | ☑ | ☑ | ☒ | ☑ |
| **PRE-BD-FEV1** | Pre-bronchodilator FEV1 | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **POST-BD-FEV1** | Post-bronchodilator FEV1 | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ | ☒ |
| **PRE-BD-FVC** | Pre-bronchodilator FVC | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **POST-BD-FVC** | Post-bronchodilator FVC | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **ALLERGEN TESTING** | Was an Environmental Allergen Test conducted? | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| | -Positive to perennial allergen (Serum Allergen Test)? | | | | | | | |
| | +Specify perennial allergen (Serum Allergen Test) | | | | | | | |
| | (Select all that apply) | | | | | | | |
| | -Positive to perennial allergen (SPT)? | | | | | | | |
| | +Specify perennial allergen (SPT) | | | | | | | |
| | (Select all that apply) | | | | | | | |
| **ASTHMA CONTROL** | Asthma Control | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ |
| **TREATMENT PLAN** | What is the current Clinical Management Plan? (Select all that apply) | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **LTOCS AND DAILY DOSE** | Is the patient prescribed Maintenance Oral Steroids? | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ |
| | Daily dose of Maintenance Oral Steroids | | | | | | | |
| **LTOCS NAME AND START DATE** | Maintenance Oral Steroid name | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Start Date of Maintenance Oral Steroids | | | | | | | |
| **PRESCRIPTION ICS+LABA/ICS/LABA/LAMA/THEO/LTRA** | Is the patient on a prescription for ICS+LABA combination therapy? | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ |
| | Is the patient on a prescription for ICS (only)? | | | | | | | |
| | Is the patient on a prescription for LABA (only)? | | | | | | | |
| | Is the patient on a prescription for LAMA? | | | | | | | |
| | Is the patient on a prescription for Theophyllines? | | | | | | | |
| | Is the patient on a prescription for Leukotrine Receptor Antagonist (LTRA)? | | | | | | | |
| | Is the patient on a prescription for Macrolide Antibiotic Treatment? | | | | | | | |
| **ICS/LABA/LAMA/Theo/LTRA start date** | Start Date of ICS+LABA combination therapy? | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| | Start Date of ICS? | | | | | | | |
| | Start Date of LABA? | | | | | | | |
| | Start Date of LAMA? | | | | | | | |
| | Start Date of Theophylline? | | | | | | | |
| | Start Date of Leukotrine Receptor Antagonist (LTRA)? | | | | | | | |
| | Start Date of Macrolide Antibiotic Treatment? | | | | | | | |
| **ICS DAILY DOSE** | ICS daily dose | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |
| **BIOLOGIC** | Prescription for Anti-Interleukin 4 (Anti-IL4) Treatment? | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ |
| | Prescription for Anti-Interleukin 5 (Anti-IL5) Treatment? | | | | | | | |
| | Prescription for Anti-IgE Treatment? | | | | | | | |
| **BIOLOGIC START DATE** | Start Date of Anti-Interleukin 4 (Anti-IL4) Treatment? | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ | ☑ |
| | Start Date of Anti-Interleukin 5 (Anti-IL5) Treatment? | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Start Date of Anti-IgE Treatment? | | | | | | | |
| **REASON FOR SWITCH** | Reason for biologic switch | ☑ | ☒ | ☑ | ☑ | ☒ | ☑ | ☒ |
| **ADHERENCE** | Is there evidence of poor adherence? | ☑ | ☒ | ☒ | ☑ | ☒ | ☒ | ☒ |