Protocol for the

International Severe Asthma Registry (**ISAR**) Extension, 2024 – 2026

Project Code: OPCG-2301
Version: 2.1
Date: 10 August 2025

OPC Global
5 Coles Lane, Oakington,
Cambridge, CB24 3BA
T: +44 1223 967855
E: info@optimumpatientcare.org
www.optimumpatientcare.org

OPCG's research partner:
OPRI Pte Ltd
22 Sin Ming Lane, #06-76,
Midview City, Singapore 573969
T: +65 3105 1489
E: info@opri.sg

Chief Investigator:

Professor David Price, Professor of Primary Care Respiratory Medicine and OPRI Director
Observational & Pragmatic Research Institute
Office address: 22 Sin Ming Lane, #06-76, Midview City, Singapore 573969
Mobile: +65 8282 2594
Email: david@opri.sg

Project Manager:

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 Co-funder:

OPC Global
AstraZeneca

Primary AZ Contact:

Trung Tran [trung.tran1@astrazeneca.com]

Table of Contents

KEY UPDATES FROM THE INITIAL ISAR PROTOCOL

This protocol is applicable to the ISAR Extension period of January 2024 to December 2026. It is an update of the initial ISAR protocol, which applied to the 6-year period of 2017 to 2023[1].

Responsible Parties

- The list of responsible parties from AstraZeneca and Optimum Patient Care Global (OPCG) has been updated *(page 7)*.

ISAR Steering Committee and Countries

- The list of ISAR Steering Committee (ISC) members and number of countries involved in ISAR have been updated *(page 11)*.

Background and Rationale

- ISAR's achievements since its establishment in 2017 are summarized, with notable research findings highlighted *(page 13)*.

Objectives

- Research objectives have been updated and quality improvement objectives added *(page 15)*.

Methodology

- The patient recruitment target and registry follow-up requirement of the ISAR Extension are outlined *(page 16)*.

Database

- The key research variables and core variables from the Delphi exercise 2024 are summarized *(page 19)*. They are listed in full in the Appendix *(page 27)*.

Research and Quality Improvement

- The quality improvement goals of the ISAR Extension have been added *(page 21)*.

Dissemination and Communication

- The updated ISAR publication principles and process are detailed *(page 22)*.

Milestones and Planned Timelines

- The milestones and planned timelines of the ISAR Extension are shown *(page 23)*.

[1]The 6-year period from 2017 included one additional year of funding from the post-authorization safety study (PASS) study of benralizumab.

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ADEPT	Anonymised Data Ethics and Protocol Transparency
AIRQ	Asthma Impairment and Risk Questionnaire
BEC	Blood eosinophil count
DSA	Data Sharing Agreement
EDC	Electronic data capture
EMA	European Medicines Agency
FDA	Food and Drug Administration (United States)
FeNO	Fractional exhaled nitric oxide
HMA	Head of Medicines Agencies
ICD	International Classification of Diseases
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled corticosteroids
ICU	Intensive care unit
IgE	Immunoglobulin E
IL4/13	Interleukin 4/13
IL5	Interleukin 5
IL5Rα	Interleukin 5 receptor alpha
ISAR	International Severe Asthma Registry
ISO	International Organization for Standardization
LABA	Long-acting beta-agonists
LAMA	Long-acting muscarinic antagonists
LTRA	Leukotriene receptor antagonists
OCS	Oral corticosteroids
OPCG	Optimum Patient Care Global
OPRI	Observational and Pragmatic Research Institute
PEF	Peak expiratory flow
Pre-BD FEV_1	Pre-bronchodilator forced expiratory volume in 1 second
Post-BD FEV_1	Post-bronchodilator forced expiratory volume in 1 second
Pre-BD FVC	Pre-bronchodilator forced vital capacity
Post-BD FVC	Post-bronchodilator forced vital capacity
REG	Respiratory Effectiveness Group

SABA	Short-acting beta-agonists
SCS	Systemic corticosteroids
SNOMED CT	Systematized Nomenclature of Medicine Clinical Terms
TSLP	Thymic stromal lymphopoietin

RESPONSIBLE PARTIES

Name	Professional Title	Role in Project	Affiliation	Email address
Trung Tran	Senior Director, Biopharmaceutical Medicine	Oversight	AZ, USA	trung.tran1@astrazeneca.com
Cathy Emmas	Head Medical and Payer Evidence Strategy, Respiratory and Immunology	Oversight	AZ, USA	cathy.emmas@astrazeneca.com
Emma Ramsden	Global Medical Affairs, Biopharmaceutical Medicine	Operational Lead	AZ, USA	emma.ramsden@astrazeneca.com
Andrew Menzies-Gow	Vice President, Respiratory and Immunology, Global Biopharmaceuticals Medical	Medical Lead	AZ, UK	andrew.menzies-gow@astrazeneca.com
Benjamin Emmanuel	Director, Evidence Strategy, Epidemiology	Epidemiology Lead	AZ, USA	benjamin.emmanuel@astrazeneca.com
Amy Pasqua	Global Corporate Affairs	Corporate Affairs Lead	AZ, USA	amy.pasqua@astrazeneca.com
Carrie Lancos	Director, Biopharmaceutical Medicine Evidence Publications	Publications Lead	AZ, USA	carrie.lancos@astrazeneca.com
Amit Parulekar	Global Medical Affairs Leader, Respiratory Biologics	Medical Affairs Lead	AZ, USA	amit.parulekar@astrazeneca.com
Siew Lee Grand-Clement	Global Medical Director – PRECISION	Medical Lead	AZ, USA	siewlee.grandclement@astrazeneca.com
David Price	Professor of Primary Care Respiratory Medicine and OPRI Director	Chief Investigator	OPRI, Singapore	david@opri.sg
Victoria Carter	Research and Operations Director	Project Manager	OPRI, Singapore	victoria@opri.sg
Chris Price	Commercial and Legal Director	Legal and Contracting Lead	OPCG, Cambridge, UK	chris.price@optimumpatientcare.org
Sophie Harriman	Legal and Relationship Manager	Legal and Collaborator Support	OPCG, Cambridge, UK	sophie.harriman@optimumpatientcare.org
Veronica Mendez	ISAR Project Manager	Project Coordinator	OPCG, Cambridge, UK	veronica.mendez@opri.sg

Harika Gosala	ISAR Project Assistant	Operational Support	OPCG, Cambridge, UK	harika.gosala@opri.sg
Pui Yee Lai	Academic Assistant	Publications Support	OPRI, Singapore	puiyee.lai@opri.sg
Karen Hosking	Data Analytics Manager	Data Analytics Lead	OPCG, Cambridge, UK	karen.hosking@optimumpatientcare.org
Angelica Tatam	Senior Data Analyst	Data Analytics Support	OPCG, Cambridge, UK	angelica.tatam@optimumpatientcare.org
Aaron Beastall	Data Analyst	Data Analytics Support	OPCG, Cambridge, UK	aaron@optimumpatientcare.org
John Busby	Head of Medical Epidemiology	Epidemiology Lead	OPCG, Cambridge, UK	john.busby@optimumpatientcare.org
Ghislaine Scelo	Senior Epidemiologist	Epidemiology Support	OPCG, Cambridge, UK	ghislaine@opri.sg
John Townend	Senior Statistician	Statistical Lead	OPCG, Cambridge, UK	john@opri.sg
Lakmini Bulathsinhala	Global Research Manager	Research Lead	OPRI, Singapore	lakmini@opri.sg
Kirsty Fletton	Medical Scientist	Research Support	OPCG, Cambridge, UK	kirsty.fletton@optimumpatientcare.org
Dominic Friston	Medical Scientist	Research Support	OPCG, Cambridge, UK	dominic.friston@optimumpatientcare.org
Celine Goh	Medical Scientist	Research Support	OPCG, Cambridge, UK	celine.goh@optimumpatientcare.org

PROJECT DELIVERY COLLABORATORS

Optimum Patient Care Global (OPCG)

OPCG (www.opcglobal.org/) is the co-funder, data custodian, and registry creator and manager. Its roles include funding the initial set-up and extension of ISAR, providing data procurement, harmonization, and hosting services for the registry, producing and providing dashboards and quality improvement reports, managing and coordinating the operations of the registry, checking and improving data quality, liaising with participating countries and sites, and managing and running an annual steering committee meeting.

OPCG provides a range of services to translate research into clinical practice, and oversees and manages new sustainable global data sources. It specialises in delivering primary and secondary care research, clinical support services, national and international quality improvement programmes, bespoke datasets for academic research and global registry projects. ISAR is the first global adult severe asthma registry, with prospective and retrospective data from >34,000 patients across 29 countries (as of June 2025). Since its establishment in 2017, ISAR has provided sufficient statistical power for severe asthma research in adults; its 26 research projects have resulted in 35 publications and 63 abstracts (as of June 2025).

Observational and Pragmatic Research Institute (OPRI)

OPRI (www.opri.org.uk/) is OPCG's research partner. Its role is to develop the research program and deliver research outputs, including study protocols, statistical analyses, reports and publications. It will also manage and coordinate the authorship review process for manuscripts, and liaise with the steering committee members.

OPRI is a research institute that provides expertise in real-life research, pragmatic clinical trials, observational studies, epidemiology, biostatistics and medical writing. It accesses unique global data sources to deliver observational and pragmatic research which drives change in clinical practice around the world. It has delivered more than 150 projects, including pragmatic trials, implementation studies, retrospective database studies and post-authorisation safety studies.

AstraZeneca

AstraZeneca is the co-funder. Its role is to fund the initial set-up and extension of ISAR, and collaborate on the pre-defined research priorities. It has three seats on the ISAR steering committee, with one combined vote.

Respiratory Effectiveness Group (REG)

The REG (www.regresearchnetwork.org/) is OPCG and OPRI's academic partner. Its role is to provide a forum for research discussion and prioritization (e.g., at the annual REG summits), and to uphold ethical standards for real-life research via the Anonymised Data Ethics and Protocol Transparency (ADEPT) committee.

REG aims to:

- Provide ethical and scientific review of real-life research study protocols
- Communicate best practice, establishing quality standards through its research and activities, and leading in providing examples of excellence in real-life research
- Establish quality standards in the field of real-life research

- Improve understanding of the important role of real-life data in informing meaningful clinical practice guidelines as well as drug licensing and post-marketing surveillance processes, and in improving patient care
- Focus on specific disease topics to generate initiatives and research in this area.

The REG is a not-for-profit investigator-led academic initiative which comprises more than 420 respiratory/allergy experts and key opinion leaders from 40 countries. It has 14 working groups, including the Biomarkers and Severe Asthma Working Group.

ISAR STEERING COMMITTEE

The ISAR Steering Committee (ISC) drives the delivery of the registry globally. Their collective clinical expertise and scientific knowledge form an essential element of the ISAR initiative. The ISC representatives of the 30 countries participating in ISAR, and of OPCG and AstraZeneca, are shown below.

Country	ISC member(s)
Argentina	Dr Jorge Maspero
Belgium	Prof Florence Schleich
Brazil	Dr Paulo Pitrez
Bulgaria	Prof George C. Christoff; Prof Todor A. Popov
Canada	Dr Celine Bergeron
Colombia	Dr Carlos A. Torres-Duque
Denmark	Dr Celeste Porsbjerg
Estonia	Prof Alan Altraja
Ecuador	Dr Ivan Cherrez Ojeda
France	Prof Camille Taillé; Prof Arnaud Bourdin
Germany	Dr Christian Taube
Greece	Prof Nikos Papadopoulos; Dr Andriana Papaioannou
India	Dr Sundeep Salvi
Ireland	Prof Richard W. Costello; Dr Patrick Mitchell
Italy	Prof Walter Canonica; Prof Enrico Heffler
Japan	Prof Takashi Iwanaga
Kuwait	Dr Mona Al-Ahmad
Mexico	Dr Désirée Larenas-Linnemann
Netherlands	Dr Job van Boven; Dr Maarten van den Berge
Norway	Dr Sverre Lehmann
Poland	Prof Piotr Kuna
Portugal	Prof João A. Fonseca
Saudi Arabia	Dr Riyad Al-Lehebi
Singapore	Prof Mariko Siyue Koh
South Korea	Prof Chin Kook Rhee
Spain	Dr Luis Perez-de-Llano; Dr Borja G. Cosio
Taiwan	Prof Diahn-Warng Perng
UAE	Prof Bassam Mahboub
UK	Prof Liam Heaney; Prof David Jackson; Dr Paul Pfeffer; Dr Pujan Patel
USA	Dr Eileen Wang; Prof Mike Weschler; Dr Rohit Katel; Dr Nijira Lugogo; Dr Roy Alton Pleasants
OPCG	Prof David Price
AstraZeneca	Dr Trung Tran; Prof Andrew Menzies-Gow; Dr Amit Parulekar

PROTOCOL SYNOPSIS

ISAR (www.isar.opcglobal.org/) is a global collaborative initiative to gather de-identified longitundinal real-world data from adult patients with severe asthma. The initiative is conducted by OPCG, with academic and regulatory oversight from the ISAR steering committee, research expertise from OPRI, academic support from the REG, ethical governance from the ADEPT committee of REG, and joint funding support from OPCG and AstraZeneca.

ISAR is a vital source of real-world data for severe asthma research, facilitating advancements in treatments and improving patient outcomes. Moreover, it provides a global platform for collaborative research in respiratory medicine.

Participating countries retain ownership of their data and share only de-identified patient-level data with ISAR. They collect and share key research variables and core variables determined by the Delphi 2024 exercise, which involved severe asthma experts from around the world. These countries adhere to the highest standards of real-world research, including governance by the REG task force through the ADEPT committee, registration with the HMA-EMA Catalogues of real-world data sources and studies, compliance with OPCG and OPRI standards, and the exclusion of drug-specific comparative research (there are no comparisons between individual drugs, though comparisons between drug classes are allowed).

Based on the ethical, legal and regulatory permissions for each participating country, de-identified data are collected into a central repository database for relevant dataset creation and analysis. OPCG provides particpating countries and sites with a complimentary centralised EDC system to enable data capture and input. Research datasets are formed for research studies approved and prioritized by the ISAR steering committee, as well as ethically approved by the ADEPT committee of REG.

1.0 Background and Rationale

Background

An estimated 5-10% of the total asthma population suffers from severe asthma, defined by the European Respiratory Society and American Thoracic Society's guidelines as asthma that requires high-dose inhaled corticosteroids (ICS) plus a second controller and/or oral corticosteroids (OCS) to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy (1). The economic burden of severe uncontrolled asthma is disproportionally higher than that that of non-severe asthma (2).

In patients with severe asthma, regular systemic corticosteroid (SCS) use is associated with adverse outcomes, including type 2 diabetes, osteoporosis, cardiovascular disease and obesity (3). A dose-response relationship for cumulative SCS exposure with adverse outcomes began at 0.5-<1 gram, equivalent to four lifetime SCS courses (4). The Global Initiative for Asthma (GINA) states that "even occasional short courses of OCS are associated with increased risk (osteoporosis, diabetes, cataract etc)" (5). Therefore, there is a need to reduce the steroid burden of patients with severe asthma.

Heterogeneous severe asthma endotypes and phenotypes have been described. Most patients with severe asthma have Type 2 inflammation, characterized by increased blood eosinophils and fractional exhaled nitric oxide (FeNO), with possible atopy and elevated IgE (6). The eosinophilic asthma phenotype is associated with more comorbidities, increased exacerbations and greater healthcare resource utilization compared with the non-eosinophilic phenotype (7).

Type 2-targeted treatments are licensed for severe asthma. Biologics approved by the United States Food and Drug Administration (FDA) for severe asthma are listed in the table (8–12).

FDA approved biologic (as of June 2025)	**Indication: Asthma**
Omalizumab (Anti-IgE)	Moderate-to-severe; allergic; ≥6 years
Mepolizumab (Anti-IL5)	Severe; eosinophilic; ≥6 years
Benralizumab (Anti-IL5Rα)	Severe; eosinophilic; ≥6 years
Dupilumab (Anti-IL4/13)	Moderate-to-severe; eosinophilic or OCS-dependent; ≥6 years
Tezepelumab (Anti-TSLP)	Severe; ≥12 years

Rationale

As a global registry, ISAR standardizes data collection and provides sufficient statistical power to study the disease burden, epidemiology, outcomes, and clinical management of adult severe asthma (13–15). It offers structured clinical guidance, assisting clinicians in identifying patients with Type 2 phenotypes who are suitable for biologics, and facilitates the evaluation of the real-world effectiveness and safety of these treatments.

Since its establishment in 2017, ISAR has received retrospective and prospective data from >34,000 patients across 29 countries; its 26 research projects have resulted in 35 publications and 63 abstracts (as of June 2025). Notable ISAR research findings include:

- the predominance of the eosinophilic phenotype in adult severe asthma (16),
- the under-recognition of patients with potential severe asthma in primary care in the United Kingdom (17),
- the increased chance of achieving remission post-biologic treatment among patients with less severe impairment and shorter asthma duration at biologic initiation (18),

- the role of biologics in preventing cardiovascular and other systemic adverse outcomes in patients with severe asthma (19),
- the effectiveness of biologics in minimizing the steroid burden of patients with severe asthma (20),
- the association between biologic initiation and improved outcomes among severe asthma patients with high OCS exposure (21),
- the superiority of Anti-IL5/5R versus Anti-IgE in reducing asthma exacerbations and long-term OCS use among severe asthma patients eligible for both (22),
- the predictive value of certain Type 2 comorbidities on biologic effectiveness in severe asthma (23),
- the real-world biologic use patterns and associated clinical outcomes in patients with severe asthma (24,25),
- the disease burden of patients with severe asthma by biologic eligibility status (26),
- the variations in ease of access to biologics across countries (27).

As part of the ISAR Extension (2024-2026), the registry has started to implement quality improvement initiatives that help ISAR countries optimize data quality and minimize OCS use among their patients.

2.0 Objectives

The purpose of ISAR is to standardize data collection and pool data internationally to answer key research questions in adult severe asthma, in order to improve outcomes for patients in a sustainable way.

Research Objectives

The research objectives of ISAR are to:

- Serve as a platform for real-world research in severe asthma, to provide insights into the disease burden, epidemiology, outcomes, and clinical management of adult severe asthma
- Describe and characterise the severe asthma population, including the evaluation of phenotypes and biomarkers
- Assess the real-life effectiveness and safety of treatments, including biologics and their impact on changing the asthma trajectory (e.g., response and remission).

Quality Improvement Objectives

The quality improvement objectives of ISAR are to:

- Improve data quality and optimize the collection of key research variables
- Embed data collection into routine clinical care and provide interactive, longitudinal feedback to clinicians and patients
- Reduce and/or eliminate long-term OCS and frequent intermittent OCS use
- Improve patient outcomes through structured asthma reviews (short-term) and increased understanding of severe asthma (long-term).

3.0 Methodology

Registry Design

ISAR is a global, multicentre registry that collects retrospective and prospective data from patients with adult severe asthma. It provides standardized annualized recording of a set of key research variables and core variables derived from the Delphi exercise 2024 that was completed by respiratory experts globally (15).

All participating countries must agree to allow output data from their respective registries to be used for collaborative independent research recommended and approved by the ISAR Steering Committee and ADEPT. For each year of the ISAR Extension (2024-2026), there are two core research studies, one of which is prioritized by the ISC and the other prioritized by AstraZeneca (and approved by the ISC). Countries may choose whether or not to participate in any additional academic studies (non-core research studies) without affecting their status as ISAR participants.

Additionally, for each year of the ISAR Extension, a quality imrovement goal is set by the ISC. The goal for 2024 is to collect 100% of key research variables while that for 2025 is to eliminate long-term OCS and frequent intermittent OCS use. The goal for 2026 is to be confirmed.

Data Collection

Based on the ethical, legal and regulatory permissions for each participating country, de-identified data are collected into a central repository database for relevant dataset creation and analysis. OPCG provides particpating countries and sites with a complimentary centralised EDC system (utilsing REDCap) to enable data capture and live feedback, based on the currently agreed Delphi variables. It is not an essential requirement to use the provided EDC system; some countries use bespoke data capture systems.

By using the centralised EDC system, countries and sites are provided with a system which has the following benefits:

- A central system that can be used to incorporate quality improvement considerations at the point of care for participating clinicans, for longer-term sustainability;
- Country profile can be controlled by a coordinating admin (for example, to enable standard prescription to be auto-filled); these defaults help improve data input and accuracy;
- Certain data-points can be pre-filled utilising patient questionnaires ahead of visits; and
- Intelligent imputations can be applied during visits for improved data quality (for example, the check of exacerbations against hospital admissions at the point of care).

Patient Population

ISAR will comprise adult patients with severe asthma who receive care at secondary and tertiary care centres in each country, in accordance with local regulatory/ ethical requirements. The target of the ISAR Extension (2024-2026) is to enrol 4,500 new patients with high-quality data. This includes the enhanced collection of data from patients receiving specific biologic therapy such as Tezepelumab.

Informed consent will be obtained from patients, to enable data sharing for research scientifically approved by the ISC and ethically approved by the ADEPT committee. The ADEPT committee, commissioned by the REG, governs the standard of database research.

Inclusion Criteria

- Aged ≥18 years at the time of enrolment
- Informed consent provided by patients
- Severe asthma:
    - Receiving GINA 2018 Step 5 therapy, *or*
    - Has 'uncontrolled' asthma on GINA 2018 Step 4 therapy (28).

Uncontrolled asthma is defined the European Respiratory Society and American Thoracic Society's guidelines as having severe asthma symptoms[2] and frequent severe asthma exacerbations requiring ≥2 bursts of systemic corticosteroids (>3 days course each) in the previous year (1).

For adults, GINA 2018 Step 4 therapy consists of medium/high-dose maintenance ICS-LABA with as-needed SABA or low-dose ICS-formoterol. GINA 2018 Step 5 therapy indicates referral for add-on treatment (e.g., tiotropium ± biologics ± low-dose OCS) with as-needed SABA or low-dose ICS-formoterol (28).

Registry Follow-up

Patients enrolled in ISAR will be followed up during routine clinical visits for a total duration of up to 8 years. Although it is anticipated that a patient visits a secondary or tertiary care clinic at least once a year, there is no interference with the routine clinical care of the patient and follow-up visit number per patient is conditional to his or her own healthcare utilization level. A follow-up visit must be 11+ months since the previous visit to be considered in data quality reviews. As the registry is real-life in nature, loss to follow-up may occur.

Specific variables will be collected at follow-up visits, as determined by the Delphi 2024 exercise (15).

[2] Severe asthma symptoms (ERS/ATS guidelines):
(a) Poor symptom control where ACQ >1.5, ACT <20
(b) Airflow limitation: FEV1 <80% predicted (pre-bronchodilator)
(c) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year

4.0 Database

Data Acquisition

A Data Sharing and Licence Agreement (DSA) with each country or site governs the:

- Method of transmission and storage of data
- Data quality assessments
- Data security and compliance with OPCG data security standards
- List of variables required for extraction from each country-specific database
- Oversight that resides with OPCG to ensure confidentiality of data received
- Remote retrieval and appraisal of data from each country to be conducted by OPCG.

Training sessions and materials are provided to countries that utilize the ISAR REDCap Cloud data capture system.

Data Management

A data management plan describes all functions, processes and specifications for data collection, extraction, delivery, cleaning and validation; it also outlines the responsibilities of personnel such as the data manager and coordinator. Concurrent manual data validation processes are performed based on parameters dictated by the plan. All modifications to the data are recorded in an audit log. All data transfers and disputes are documented. High data quality standards (ISO 9001 - the world's most recognised Quality Management System Standard) are maintained, to ensure that the data are as accurate as possible when used in study analyses.

OPCG will continue to hold de-identified data in the ISAR Central Data Repository or Database in perpetuity unless the participating country or site notifies OPCG in writing to destroy the data, subject to any applicable legal requirements for data retention. Please note it is not possible to remove a patient's data from anonymised research data or datasets, results or publications, as the patient cannot be identified in order to remove them. A participating country or site can request at any time for their patients' data to be removed from OPCG databases without disclosing the identity of patients; subject to any requirements on data retention by applicable data law(s).

Registry Coding

All data collected by participating countries must comply with the standardised clinical codes and terms in the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) dictionary which is becoming the recognised clinical successor to the International Classification of Diseases (ICD) and Read coding that can provide the level of detail required for the coding purposes of the registry. Ideally the data coding should be consistent with other medical coding systems used in clinical practice to avoid duplication.

Delphi-derived Variables

The Delphi process is an iterative method of questioning that assumes group judgments are more valid than individual judgments (29). The anonymity of the participants ensures that all opinions are considered equally.

Initial Delphi exercise 2017

At the establishment of ISAR in 2017, ISC members agreed on a list of 95 core variables that countries are required to collect. Variable categories included demographics, medical history, asthma control, spirometry, biomarkers, type 2 comorbidities and asthma medications (14).

Delphi exercise 2024

A second Delphi exercise was carried out in 2023–2024 for ISC members to re-prioritize and refine the variables for collection (15). The ISC decided on 31 key research variables and 63 core variables.

- **Key research variable list**: to ensure high-quality data usable in research, 100% collection of key research variables is required.
    - Examples include exacerbations, asthma control, spirometry, use of long-term OCS and biologics.
- **Core variable list**: ≥90% collection of core variables is required.

The full list of key research variables and core variables can be found in the Appendix.

For patients receiving biologics, countries are required to collect pre-biologic variables (within 1 year prior to biologic initiation). Pre-biologic variables include biomarkers, exacerbations, asthma control, spirometry, and long-term OCS use.

Variables that can be optionally collected by countries, based on their own specific interests (30). Examples include:

- Validated asthma control tests:
    - Asthma Control Test (ACT)
    - Asthma Control Questionnaire (ACQ)
    - Asthma Impairment and Risk Questionnaire (AIRQ)
- Steroid-related comorbidity variables:
    - Examples include type 2 diabetes, osteoporosis, cardiovascular events, obstructive sleep apnoea and anxiety/depression
- Safety variables possibly associated with biologic initiation:
    - Anaphylaxis
    - Serious infections
    - Cancer.

Electronic data capture

All participating sites are responsible for extracting and de-identifying batches of patient data for a specific data collection time frame from their current electronic data capture systems. OPCG ensures data security (ISO 27001 - the world's most recognised Information Security Management Standard). OPCG is responsible for importing, harmonizing and integrating data into the central ISAR data repository. Data are held with a unique patient Identification Number (ID) but stored in a de-identified way.

Data Ownership

Each participating country owns their country-specific data. The extraction and integration of datasets for ethically approved research studies are managed by OPCG.

Data Access and Governance

Scientific Governance: The regulation of the registry is under the jurisdiction of the ISC. The ISC determines the scientific and research merits of any research proposal to access and/or use de-identified data from ISAR.

Ethical Governance: Applications approved by the ISC undergo ADEPT review for ethics and governance approval. The ADEPT committee provides ethical governance of the data.

Data Procurement: Upon receipt of governance approval and subject to the recipient entering into a strict data sharing and licence agreement, OPCG transfers de-identified data by way of an analytical dataset from the central ISAR database according to the data specifications/ requirements approved by ADEPT.

5.0 Research and Quality Improvement

Research ethical approval and process

In joining the ISAR network, all countries as a minimum, must agree to allow output data from their respective registries for collaborative independent research recommended by the ISC and ethically approved by ADEPT.

The ISC holds annual meetings at the REG summits to ensure that research and quality improvement objectives are achieved.

Research objectives

For each year of the ISAR Extension (2024-2026), there are two core research studies proposed by the ISC. One of them is prioritized by the ISC and the other is prioritized by AstraZeneca (and approved by the ISC).

For the core research studies, the funding covers the following components:

- **Protocol**: documented overview of a proposed study as designed in relation to its objectives and research questions. This would include study background, research objectives, study design, methodology etc.
- **Data procurement**: development of systems and processes to facilitate the collection of standardised data variables from individual patients, sites and countries to contribute to the ISAR registry.
- **Dataset creation**: a specific sub-set of the registry data (dataset) created as per the data specification set out in a given research proposal/protocol as approved by the ISC and ADEPT.
- **Data and statistical analysis**: examination, summarization, manipulation, and interpretation of the dataset to answer any approved research question.
- **Study report**: communication of the results and conclusions of approved research studies, including the methodology used, the data collected, and statistical results drawn from that data.
- **Publication**: distribution of research results to the wider community via peer reviewed journals (manuscripts) and international conferences (abstracts). This is intended to further the progress of science in any given research field.

Additionally, ISAR ‘gives’ countries back their data, providing countries with opportunities to use the data for local or regional research and publications.

Quality improvement objectives

For each year of the ISAR Extension, a quality improvement goal is set by the ISC. The goal for 2024 is to collect 100% of key research variables while that for 2025 is to eliminate long-term OCS and frequent intermittent OCS use. The goal for 2026 is to be confirmed.

ISAR provides countries with tools that help facilitate their quality improvement objectives of optimizing data quality and eliminating steroid use. Examples of tools include:

- ISAR REDCap Cloud data capture system, which is structured according to the flow of the clinical consultation and embeds data collection into routine clinical care
- Instant patient care reports, which summarize the patient’s asthma journey
- QISAR dashboards, which provide clinicians with longitudinal feedback on patient demographics, clinical outcomes and data quality.

6.0 Dissemination and Communication

Publication principles and process

The publication principles and process are detailed in the ISAR Research and Publications Charter (April 2024). Manuscript and abstract drafts are delivered to the ISC and qualified authors, then first round of revisions, repeat review and revisions are conducted. Final drafts are shared with all authors for approval, and subsequently submitted to journals or congresses identified by the authors and/or ISC. A copy of all peer-reviewed publications is submitted to the ADEPT Secretariat.

Examples of congresses:

- European Respiratory Society (ERS) congress
- American Thoracic Society (ATS) congress
- Respiratory Effectiveness Group (REG) summit
- Asian Pacific Society of Respirology (APSR) congress

Examples of journals:

- American Journal of Respiratory and Critical Care Medicine
- Journal of Allergy and Clinical Immunology: In Practice
- Journal of Asthma and Allergy
- CHEST
- Pragmatic and Observational Research
- The Lancet Regional Health

All authors agree to comply with the International Committee of Medical Journal Editors (ICMJE) criteria regarding authorship, and to disclose any potential conflicts of interest. The order of authors will be based on the following principles:

- First author should be the project lead who has had the most contribution to the study concept, design and execution of the project; the last author has had overall oversight of the respective study. Second and third author positions reflect notable contribution to the publication.
- For AZ-collaborative and ISC studies, all other authors will be listed alphabetically by country and within each country, each author will be listed alphabetically by surname.
- Individuals who fulfill ICMJE authorship criteria, but who are not represented in the main authorship list because of journal authorship limits, will be recognised in the study group list. This is regarded as full authorship status.
- Individuals who contributed data to the research study, but who do not fulfil ICMJE authorship criteria, will be included in the acknowledgements.

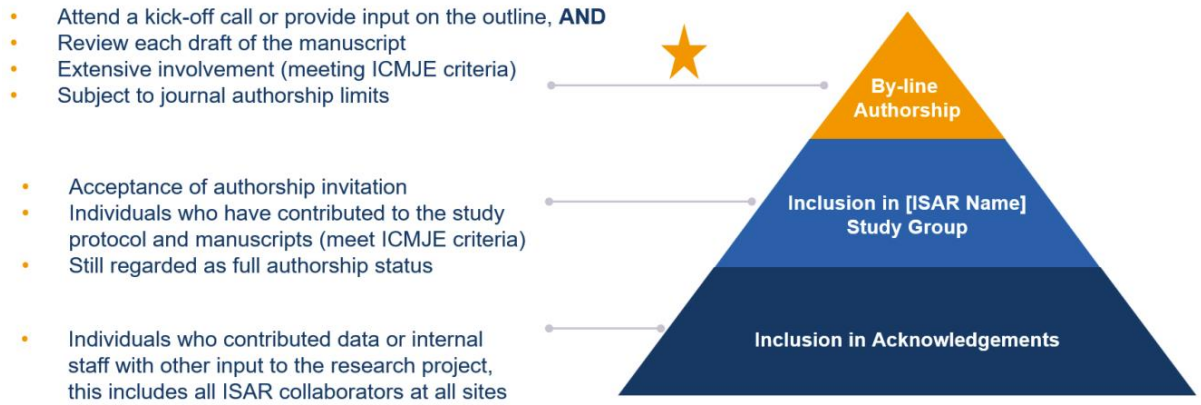

Figure: Authorship criteria for ISAR publications

7.0 Milestones and planned timelines

Milestone	Planned timeline
Full contract signature	July 2023
Commencement of ISAR extension	January 2024
Draft protocol for ISC-prioritized study 1	February 2024
Production of dataset for ISC-prioritized study 1	June 2024
Study analysis for ISC-prioritized study 1	September 2024
Draft protocol for ISC-prioritized study 2	February 2025
Production of dataset for ISC-prioritized study 2	June 2025
Study analysis for ISC-prioritized study 2	September 2025
Draft protocol for QI study	January 2026
Draft protocol for ISC-prioritized study 3	February 2026
Production of dataset for QI study	April 2026
Production of dataset for ISC-prioritized study 3	June 2026
Study analysis for QI study	July 2026
Study analysis for ISC-prioritized study 3	September 2026
4,500 new ISAR patients with high-quality data	October 2026

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9.0 Appendix

ISAR key research variables and core variables

The full list of key research variables and core variables in ISAR is shown below. The key research variables are highlighted in yellow; 100% data coverage is required to ensure high-quality data usable in reseach. For the core variables, ≥90% data coverage is required.

Baseline visit		Follow-up visits	
Core variable[a] data categories and fields	**Key[b]**	**Core variable[a] data fields**	**Key[b]**
Patient details			
On GINA 2018 Step 5 asthma treatment, or uncontrolled[c] on Step 4?			
Visit date		✓	
Birth date		✓	
Gender		✓	
Weight		✓	
Height		✓	
Ethnicity		×	
Current occupation		×	
Medical history			
Smoking status		✓	
Pack years (if indicated for ex-smoker or current smoker)[d]		✓	
Years since last smoked (if indicated for ex-smoker)		Date patient quit (if indicated for ex-smoker)	
Age at asthma onset[e]		×	
Exacerbation assessment			
Total exacerbations requiring rescue steroids in past 12 months		Total since last visit	
Total ever episodes of invasive ventilation		×	
Total emergency hospital visits for asthma in past 12 months		Total since last visit	
Total hospital admissions for asthma in past 12 months		Total since last visit	
Relevant comorbidity			
Indication of eczema		✓	
Indication of allergic rhinitis		✓	
Indication of chronic rhinosinusitis		✓	
Indication of nasal polyps		✓	
Diagnosis of osteoporosis		✓	
Date of osteoporosis diagnosis		✓	
Diagnosis of type 2 diabetes		✓	
Date of type 2 diabetes diagnosis		✓	
Blood counts			
Highest blood eosinophil count in past year		Highest count since last visit	
Date of highest blood eosinophil count in past year		Date of highest count since last visit	
Current/latest blood eosinophil count		✓	
Latest IgE count		×	
Date of immunoglobulin E count		×	
Lung function			
Pre-bronchodilator FEV_1 (actual or predicted %)[f]		✓	
Post-bronchodilator FEV1 (actual or predicted %)		✓	
Pre-bronchodilator FVC (actual or predicted %)[f]		✓	
Post-bronchodilator FVC (actual or predicted %)		✓	
FEV1/FVC ratio pre-bronchodilator[d]		✓	
FEV1/FVC ratio post bronchodilator[d]		✓	

Baseline visit		Follow-up visits	
Core variable[a] data categories and fields	**Key[b]**	**Core variable[a] data fields**	**Key[b]**
Was fractional exhaled nitric oxide test done?		✓	
Date of fractional exhaled nitric oxide test		✓	
Fractional exhaled nitric oxide test result[g]		✓	
Allergen testing			
Was an environmental allergen test done?		×	
Serum allergen/skin prick test result positive to perennial allergen?		×	
Specify serum allergen/skin prick test positive perennial allergen		×	
Asthma control			
Asthma control[h]		✓	
Current clinical management plan		✓	
Asthma medications: oral corticosteroids			
Is the patient being prescribed long-term oral corticosteroid?		✓	
Daily dose of long-term oral corticosteroid		✓	
Name of long-term oral corticosteroid		×	
Start date of long-term oral corticosteroid		✓	
Asthma medications: background therapies			
Is the patient being prescribed ICS + LABA?		Has ICS + LABA therapy changed?	
Is the patient being prescribed ICS only?		Has ICS only therapy changed?	
Is the patient being prescribed LABA only?		Has LABA only therapy changed?	
Is the patient being prescribed LAMA?		Has LAMA therapy changed?	
Is the patient being prescribed a theophylline?		Has theophylline therapy changed?	
Is the patient being prescribed LTRA?		Has LTRA therapy changed?	
Is the patient being prescribed a macrolide antibiotic?		Has macrolide antibiotic therapy changed?	
Start date of ICS+LABA/ICS only/LABA only/LAMA/theophylline/ LTRA/macrolide antibiotic		✓	
Daily dose of inhaled corticosteroids		✓	
Asthma medications: biologic agents			
Is the patient being prescribed anti-IL4?		Has anti-IL4 therapy changed	
Is the patient being prescribed anti-IL5		Has anti-IL5 therapy changed	
Is the patient being prescribed anti-IgE?		Has anti-IgE therapy changed	
Start date of anti-IL4/anti-IL5/anti-IgE		✓	
Has the patient switched biologic therapies?		✓	
Reason for switching biologic therapy		✓	
Adherence			
Is there evidence of poor adherence?		×	

GINA, Global Initiative for Asthma; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; ICS, inhaled corticosteroids; IL4, interleukin 4; IL5, interleukin 5, IgE, immunoglobulin E..

✓ = variable is core/key at follow-up ; ✕ = variable is optional at follow-up.

[a]90% completion for core variables required.

[b]Key research variable –100% data coverage required.

[c]Uncontrolled defined as ≥1 of: poor symptom control, airflow limitation, serious exacerbations, frequent exacerbations.

[d]Automatically derived variable.

[e]Whole years or months if <1 year.

[f]All pre-bronchodilator values are to be considered 'on-treatment'.

[g]Subject to reimbursement being available.

[h]As defined by GINA guidelines.