Review

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International Severe Asthma Registry (ISAR): 2017–2024 Status and Progress Update

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Abstract

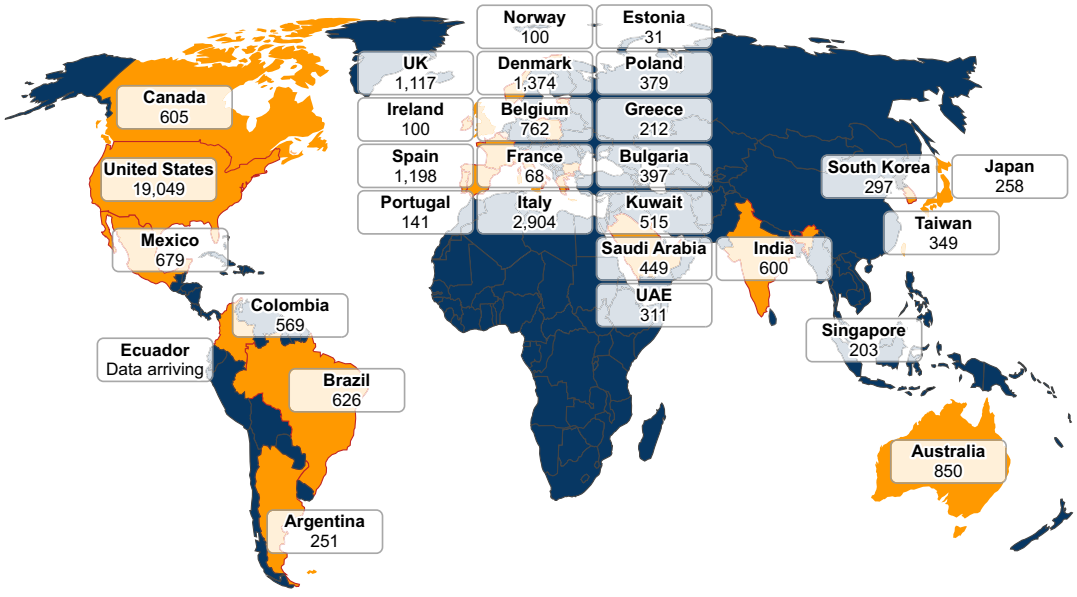
The International Severe Asthma Registry (ISAR) was established in 2017 to advance the understanding of severe asthma and its management, thereby improving patient care worldwide. As the first global registry for adults with severe asthma, ISAR enabled individual registries to standardize and pool their data, creating a comprehensive, harmonized dataset with sufficient statistical power to address key research questions and knowledge gaps. Today, ISAR is the largest repository of real-world data on severe asthma, curating data on nearly 35,000 patients from 28 countries worldwide, and has become a leading contributor to severe asthma research. Research using ISAR data has provided valuable insights on the characteristics of severe asthma, its burdens and risk factors, real-world treatment effectiveness, and barriers to specialist care, which are collectively informing improved asthma management. Besides changing clinical thinking via research, ISAR aims to advance real-world practice through initiatives that improve registry data quality and severe asthma care. In 2024, ISAR refined essential research variables to enhance data quality and launched a web-based data acquisition and reporting system (QISAR), which integrates data collection with clinical consultations and enables longitudinal data tracking at patient, center, and population levels. Quality improvement priorities include collecting standardized data during consultations and tracking and optimizing patient journeys via QISAR and integrating primary/secondary care pathways to expedite specialist severe asthma management and facilitate clinical trial recruitment. ISAR envisions a future in which timely specialist referral and initiation of biologic therapy can obviate long-term systemic corticosteroid use and enable more patients to achieve remission.

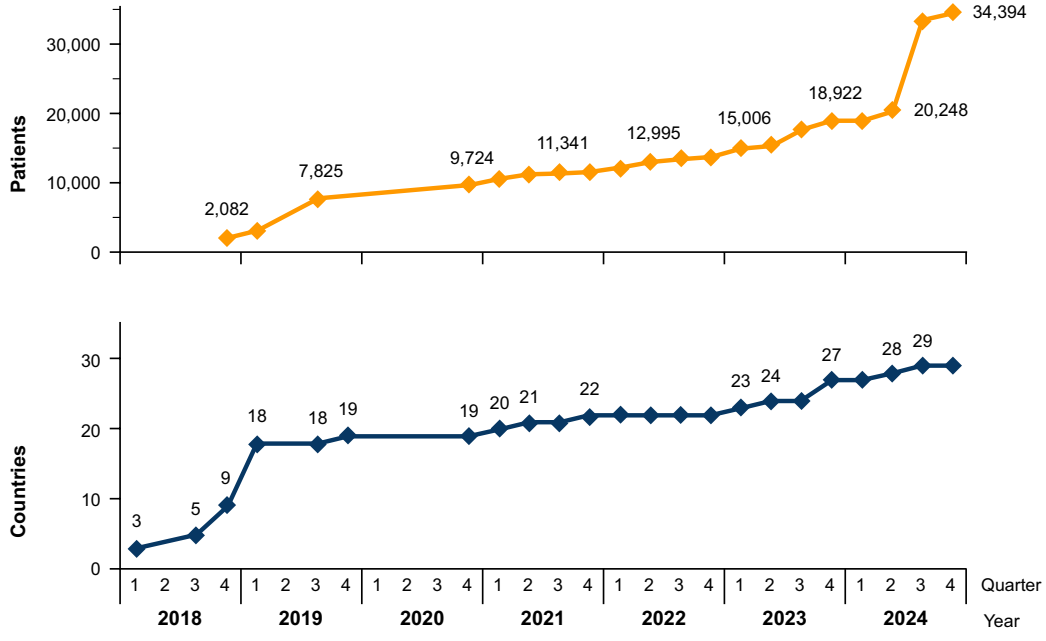
Keywords: International Severe Asthma Registry (ISAR); Optimum Patient Care Global; Core Variables; Real-World Data; Quality Improvement; Delphi Consensus

Introduction

The International Severe Asthma Registry (ISAR) is a pioneering, collaborative initiative dedicated to advancing the understanding of severe asthma and its management, with the ultimate objective of improving patient care and outcomes globally[1,2]. Since it was established in 2017, ISAR has enabled local, regional, and national registries worldwide to standardize and pool their data on adults with severe asthma, generating a comprehensive, centrally curated dataset that is shared seamlessly between stakeholders to apply existing knowledge, promote research, and gain novel insights[1,2]. Today, ISAR has expanded to become the largest and preeminent data resource for real-world studies on severe asthma; at the time of writing, ISAR curated standardized data on nearly 35,000 patients submitted by more than 250 local registries in 28 countries from all over the world (Figure 1); meanwhile, researchers have published more than 25 papers based

Figure 1. International Severe Asthma Registry (ISAR) state in the World 2017 to 2024.
UAE: United Arab Emirates; UK: United Kingdom. Map by www.freeworldmaps.net.





on ISAR data, which have provided valuable insights on the characteristics, burdens, and real-world treatment of severe asthma[1-28]. These achievements underscore global recognition of ISAR in spearheading severe asthma research[29-31]. This progress update describes ISAR's origins, organization and operation, research outputs, ongoing quality improvement (QI) program, and vision for the future.

Origins and Objectives

ISAR was conceived to address longstanding challenges. Severe asthma is a heterogenous disease that is often difficult to treat[2]—less than 25% of patients have well controlled disease despite standard-of-care treatments[5]. Although severe asthma affects a minority of all patients with asthma, it is associated with substantial morbidity and mortality, impaired psychosocial well-being and quality of life, and significant healthcare utilization and expenditure[2,4,5]. Addressing the significant unmet healthcare needs of this patient population is a priority for asthma research[3,4]. Randomized controlled trials (RCTs) are the cornerstone of evidence-based medicine, but have low external validity; real-world studies can provide complementary data on treatment effectiveness beyond highly-selective RCT patient populations[1,29,31]. RCTs in severe asthma, especially those for biologic therapies, are often unrepresentative[1,29,32]; only 5.3% of ISAR patients in one study met standard RCT inclusion criteria[27]. Registries bridge this 'efficacy-effectiveness' gap, providing valuable sources of real-world data on asthma characteristics, trends, and treatment outcomes, which can inform improved management strategies[1-3,29,31]. However, the severe asthma population is relatively small, sparsely dispersed, and heterogenous, and the fragmentary registry landscape preceding ISAR made it challenging to conduct large-scale studies and to compare data across patient populations and geographical regions[1,2]. The few existing national/regional registries were discrete and relatively small, used differing definitions of severe asthma, and collected disparate data of varying quality and completeness[1,3-5]. These limitations precluded interoperability and restricted the statistical power of single-registry severe asthma studies, depending on their patient numbers[1,2]. Responding to the clear need for a unified approach, ISAR was established to accrue a standardized global dataset from multiple registries worldwide, which would ensure data consistency, comparability, and quality, promote interoperability and collaboration, and provide ample statistical power for real-world studies to answer key clinical and research questions[1,2,4]. Importantly, this large-scale registry facilitates the identification and analysis of patient subgroups with differing characteristics and care needs, including regional differences between patients and in their management. Moreover, these data from the broad patient population in real-world practice can provide information and answer questions that are not amenable to investigation in RCTs[1,29,31]. By standardizing and consolidating comprehensive data collected from severe asthma populations worldwide, ISAR has unlocked the potential to conduct robust research that is advancing the understanding of severe asthma and contributing to the evolution of best practice in asthma management and patient care on a global scale[1,2,4,5,29,31].

1. Founding principles and mission

ISAR operates according to core guiding principles of openness, inclusivity, and collaborative data sharing and research discussions[1]; ISAR contributors own their data and share only anonymized data, collect and share specified ISAR core variables, and uphold the research standards governing ISAR. Impartiality is a fundamental precept, and the ISAR database cannot be used to conduct inferential drug-specific comparative studies[2].

ISAR's primary objectives are to characterize and describe severe asthma internationally, both in the overall patient population and among different subgroups of interest, and to facilitate phenotyping and endotyping, so that patient groups can be distinguished by their disease burden, management patterns, and clinical evolution[2]. Important secondary objectives include supporting the development of effective diagnostic/prognostic modalities, evaluating the real-world effectiveness and safety of treatments for severe asthma, and improving patient outcomes—for example, by identifying potentially modifiable factors associated with poor outcomes and implementing steroid-sparing treatments and strategies[2]. The overarching aims are to consolidate knowledge about severe asthma and support research that will improve the care of adult patients globally, whether in primary, secondary, or tertiary care[1,2]. ISAR's pursuit of these goals leverages key strengths, specifically: its global reach, inclusivity, and expertise; collecting standardized, comprehensive, and high-quality longitudinal individual-level data from countries worldwide; an organizational structure that supports robust and ethical scientific research; and extensive experience in data capture and management[1,2].

Organization, Oversight, and Operation

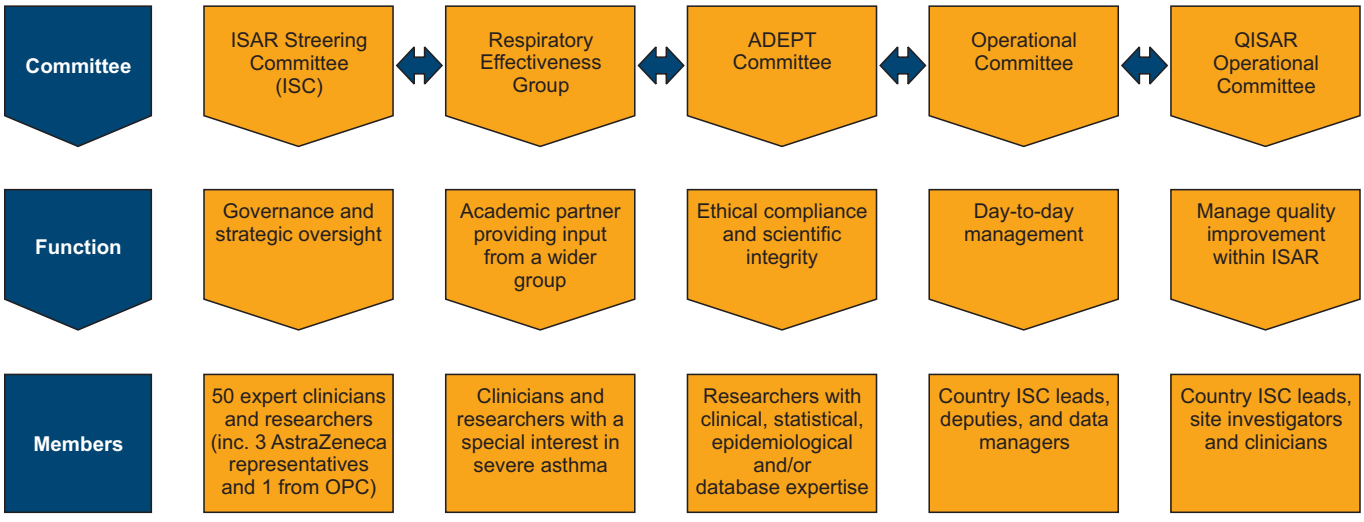
ISAR is a joint initiative of Optimum Patient Care Global Limited (OPC), a not-for-profit social enterprise, and AstraZeneca, its co-founders and sponsors since May 2017; a third core collaborator is the Respiratory Effectiveness Group (REG), an investigator-led initiative to promote real-world research[2]. OPC operates ISAR and is responsible for data management, processing and analysis, REG provides academic support, and AstraZeneca gives strategic input[2].

ISAR is governed and managed by several complementary bodies (Figure 2): the ISAR Steering Committee (ISC), the REG, the Anonymized Data Ethics & Protocol Transparency (ADEPT) Committee, an Operational Committee, and the QISAR Operational Committee. The ISC comprises 50 experts specializing in severe asthma from 31 countries across five continents, including representatives from AstraZeneca and OPC, who provide scientific leadership and regulatory and strategic oversight. The ADEPT Committee is commissioned by the REG to review the quality of ISAR research protocols and ensure that research using ISAR data complies with the highest ethical standards. The Operational Committee includes research staff in participating countries and is involved in running ISAR day-to-day[1,2]. The QISAR Operational Committee manages ISAR QI initiatives. The ISC and other key committees meet regularly to maintain continuing expert input in steering the development and expansion of ISAR, and to ensure that its research is clinically relevant, up-to-date, and delivers value to stakeholders in pursuing its mission to improve severe asthma care[2].

ISAR is open, inclusive, and actively welcomes new partnerships, offering support to establish local registries, which includes providing its standardized variables list and electronic data capture technology[1], which can be translated into local languages. ISAR participants or any third-party, including academic or commercial researchers, can submit research proposals, which require approval by both the ISC and ADEPT. All proposals are reviewed annually and prioritized based on their scientific rigor, feasibility, and compliance with ethical standards. Each member country and AstraZeneca have one vote on project selection, with OPC holding a casting vote to resolve ties. To avoid potential bias, AstraZeneca is recused from votes on proposals from other commercial entities[1,2]. Core research themes in the first years of operation have included the epidemiology and clinical characteristics of severe asthma, including comparing eosinophilic and non-eosinophilic phenotypes, and evaluating responsiveness to different classes of biologic asthma therapy[2]. The ISC's prioritized project for 2024 is a study investigating associations between differing initiation timings of biologic therapy for severe asthma, and outcomes of disease progression and the likelihood of remission.

National, regional, and local registries participating in ISAR retain ownership of their own data but allow access to and share de-identified patient data for independent research projects approved by the ISC and ADEPT, according to a data sharing agreement that

Figure 2. International Severe Asthma Registry (ISAR) organization and governance.
ADEPT: Anonymised Data Ethics & Protocol Transparency; OPC: Optimum Patient Care. This work is modified from FitzGerald et al.[2] BMC Med Res Methodol 2020;20:212. Licensed under CC BY 4.0.



details the frequency and manner of data transfer to OPC[2]. ISAR participation allows research using either ISAR multi-country data, subject to ISC and ADEPT approval, or standardized country-specific data, as member countries are free to conduct their own research based on local governance. ISAR is registered with the Heads of Medicines Agencies/European Medicines Agency Catalogues of real-world data sources.

1. Patient selection and data collection

To be included by ISAR, patients at participating centers must meet eligibility criteria, which were chosen to capture a broad population of patients with severe asthma in real-world settings, including those with moderate-to-severe asthma and not excluding those with a history of smoking[2]. Briefly, patients must be ≥18 years old and either receiving step 5 treatment according to the 2018 definitions of the Global Initiative for Asthma (GINA)[33] or have asthma 'uncontrolled' on GINA step 4 treatment, as defined by the European Respiratory Society/American Thoracic Society guidelines[34].

The first challenge that ISAR tackled was to standardize data collection by its international members and thereby enable the pooling, analysis, and robust interpretation of data across diverse patient populations and geographic and clinical settings[2]. ISC members conducted a modified Delphi process in 2017 to reach consensus on a standard set of core research variables; these comprised 95 variables in 13 categories, including demographics, medical history, clinical characteristics, lung function, biomarkers, and patient-reported outcome measures[2,3]. Collection and reporting of all specified core variables is a condition of ISAR participation[2,3]. Other standardized variables that were not included in the core set but may also be shared via ISAR or collected locally include safety and effectiveness bolt-on variables, such as adverse events potentially associated with use of biologic agents, and further optional variables deemed useful for research—for example, morbidities associated with exposure to corticosteroids, occupation, non-core biomarkers, and mental well-being or quality of life metrics[2,4].

Research Outputs and Insights from ISAR

Within just 7 years of its inception, ISAR research has already made substantive contributions to characterizing severe asthma, describing associated risk factors and burdens, assessing outcomes among different treatment groups, and accruing real-world evidence on current treatment strategies. More than 25 articles on these topics and related research were published from 2019 to 2024 (Table 1 and Figure 3).

1. Epidemiology and global burdens of severe asthma

Severe asthma is a complex, heterogeneous, and incompletely understood condition that affects 5%–10% of all patients with asthma—more than 13 million people worldwide[5,35]. Although severe asthma affects a minority of the whole asthma population, it imposes disproportionately high burdens of morbidity, mortality, and healthcare resource utilization, with substantial psychosocial and socioeconomic impacts[2,5]. In the first study to characterize severe asthma worldwide, based on data from ISAR and other registries internationally, severe asthma was estimated to account for more than 60% of total asthma-related healthcare costs, a large proportion of which are attributable to oral corticosteroid (OCS)-related morbidities[5]. Insights from ISAR that are informing improved asthma management and patient care will contribute to progress towards alleviating these burdens.

Exposure to systemic corticosteroids, which are widely used to treat asthma[36], significantly increases patients' risk of multiple adverse outcomes, such as type 2 diabetes, osteoporosis, and cardiovascular diseases, starting from doses equivalent to only four short OCS courses per lifetime (0.5 to <1 g)[37-40]. Consequently, updated GINA guidelines for difficult-to-treat and severe asthma caution that low-dose OCS should only be added as a last resort, having first optimized treatment, and where steroid-sparing biologic therapy is unavailable or unaffordable[41]. Notably, use of moderate-high doses of inhaled corticosteroids has also been associated with adverse outcomes, which included cardiovascular events, pulmonary embolism, and pneumonia[42]. The ISAR PRISM study highlighted the extent of the burden of comorbidities in severe asthma: 55% of patients had three or more comorbidities and 68% had at least one potentially OCS-related comorbidity, which included obesity (42%), hypertension (23%), dyslipidemia (16%), osteoporosis (13%), diabetes (12%), and coronary heart disease (9%); patients with OCS-related comorbidities were more likely to experience exacerbations[12]. Such evidence underpins the concept of corticosteroid stewardship, which advocates prescribing corticosteroids only when clinically justified and at the lowest effective dose, and preferentially using steroid-sparing strategies and/or non-steroid alternatives, including targeted biologics, wherever appropriate[43-45]. Besides the burdens of OCS-related morbidity, patients with severe asthma are at risk for airway remodeling due to

Table 1. International Severe Asthma Registry research project outputs and related publications

Topic area, article title (study acronym)	Key insights
ISAR & severe asthma data collection	
Development of the International Severe Asthma Registry (ISAR): a modified Delphi study[3]	Early national/region-specific asthma registries collected disparate data of varying quality. First standardized set of core severe asthma registry variables established.
International severe asthma registry (ISAR): protocol for a global registry[2]	This first global registry for adult severe asthma provides a rich real-life data resource for research to understand severe asthma better and improve patient care worldwide.
International Severe Asthma Registry: mission statement[1]	ISAR aspires to achieve global reach, standardize metrics, ensure ethical and clinically appropriate research, and disseminate findings.
Adult severe asthma registries: a global and growing inventory[4]	Standardized data collection enables registries to collect unified data and increase the statistical power of studies on severe asthma.
Severe asthma characteristics and epidemiology	
Characterization of severe asthma worldwide: data from the International Severe Asthma Registry[5]	Clinical presentations, biomarkers, and treatments vary internationally. High OCS usage and fixed airways obstruction are global problems.
Potential severe asthma hidden in UK primary care[6]*	Many UK patients with potential severe asthma are underrecognized in primary care.
Asthma exacerbations are associated with a decline in lung function: a longitudinal population-based study[7†]	Asthma exacerbations accelerate lung function decline, especially in younger patients.
Cluster analysis of inflammatory biomarker expression in the International Severe Asthma Registry (BRISAR)[8]	Biomarker positivity overlaps but distinct expression clusters suggest discrete patterns of underlying inflammatory pathway activation.
Eosinophilic and noneosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort[9]	The severe asthma eosinophilic phenotype is phenotypically distinct and more prevalent than was previously recognized.
Biomarker-defined clusters by level of type 2 inflammatory involvement in severe asthma (EMBER)[10]	Clusters varied in biomarker elevation, highlighting the complexity of T2 inflammatory involvement in severe asthma. A predominantly female cluster had low biomarker levels, suggesting low T2 involvement.
Impact of socioeconomic status on adult patients with asthma: a population-based cohort study from UK primary care (RADIANT)[11†]	Asthma control and exacerbation rates worsen with socioeconomic deprivation, yet the most deprived patients have referral rates similar to the least deprived.
Analysis of comorbidities and multimorbidity in adult patients in the International Severe Asthma Registry (PRISM I)[12]	Comorbidity/multimorbidity affects most adults with severe asthma and is associated with poorer asthma-related outcomes. Patients with OCS-related comorbidities had more frequent exacerbations.
International variation in severe exacerbation rates in patients with severe asthma[13]	Patients with similar characteristics but from different jurisdictions have varied severe exacerbation risks, suggesting that unknown patient or system-level factors are involved. Risk prediction models and guidelines should be tailored accordingly.
Individualized risk prediction model for exacerbations in patients with severe asthma: protocol for a multicentre real-world risk modelling study[14]	Developing and validating a model for predicting the risk of severe exacerbations in patients with severe asthma has potential clinical utility in guiding asthma treatment escalation.
Heterogeneity of asthma-chronic obstructive pulmonary disease (COPD) overlap from a cohort of patients with severe asthma and COPD[15]	Patients with pure severe asthma or pure chronic obstructive pulmonary disease (COPD) have similar prevalence of overlapping asthma/COPD (ACO). Patients in each group with ACO have comparable exacerbation risk and lung function impairment.

Table 1. Continued

Topic area, article title (study acronym)	Key insights
Biologic treatments: usage, responsiveness, and outcomes	
Real world biologic use and switch patterns in severe asthma: data from the International Severe Asthma Registry and the US CHRONICLE study (SUNNIE)[16]	Patients who stopped/switched biologics had comparatively lower lung function, higher baseline eosinophil count and exacerbation rate, and more healthcare resource utilization.
Global variability in administrative approval prescription criteria for biologic therapy in severe asthma (BACS)[17]	The Biologic Accessibility Score highlighted marked between-country differences in ease of access to biologic treatments.
Clinical outcomes and emergency healthcare utilization in patients with severe asthma who continued, switched or stopped biologic therapy: results from the CLEAR study (CLEAR)[18]	Biologic switchers (25.5%) or quitters (14.5%) had higher rates of exacerbations and uncontrolled asthma than patients who continued an initial biologic; switchers had a higher long-term OCS dose and more hospitalizations and emergency visits.
Comparative effectiveness of anti-IL5 and anti-IgE biologic classes in patients with severe asthma eligible for both (FIRE)[19]	Both anti-IgE and anti-IL5/5R improved asthma outcomes in eligible patients, but anti-IL5/5R more effectively reduced exacerbations and long-term OCS use.
Characterization of Patients in the International Severe Asthma Registry with High Steroid Exposure Who Did or Did Not Initiate Biologic Therapy (GLITTER I)[20]	Approximately 30% of patients with severe asthma who had high OCS exposure did not receive biologics despite a high exacerbation rate similar to that of biologics initiators.
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 (GLITTER II)[21]	Patients with high OCS use who initiated biologics had greater improvements in severe asthma outcomes, including OCS exposure, exacerbation rate and healthcare utilization, compared to others who continued long-term or frequent rescue OCS.
Association between T2-related comorbidities and effectiveness of biologics in severe asthma (PRISM II)[22]	Chronic rhinosinusitis, with or without nasal polyps, and nasal polyps alone predict the effectiveness of biologic treatments for severe asthma.
Impact of pre-biologic impairment on meeting domain-specific biologic responder definitions in patients with severe asthma (BEAM)[23]	Exacerbations, long-term OCS use, and asthma control can assess response to biologics. Responsiveness varied by domain assessed and increased with baseline impairment, which was worst in anti-IL5/5R initiators.
Association between pre-biologic T2-biomarker combinations and response to biologics in patients with severe asthma (IGNITE)[24]	Higher baseline blood eosinophil count, fraction of exhaled nitric oxide, and both together, predict biologic-associated lung function improvement.
Exploring definitions and predictors of response to biologics for severe asthma (FULL BEAM I)[25]	Many biologic responders have residual symptoms post-initiation; predictors of response vary with the outcome assessed.
Exploring definitions and predictors of severe asthma clinical remission after biologic treatment in adults (FULL BEAM II)[26]	Remission was more likely in patients with less severe asthma and shorter disease duration at baseline; biologic treatment should not be delayed if remission is the goal.
Real-world biologics response and super-response in the International Severe Asthma Registry cohort (LUMINANT)[27]	Responses/super-responses in all outcome domains were more frequent in biologic initiators than in non-initiators; however, 40–50% of biologic initiators did not meet response criteria.
Disease burden and access to biologic therapy in patients with severe asthma, 2017-2022: an analysis of the International Severe Asthma Registry (EVEREST)[28]	Patients without access to biologics or not receiving them have a substantial disease burden; many biologic recipients respond sub-optimally, with persisting exacerbations, uncontrolled asthma, healthcare utilization, and long-term OCS use.

*Study analyzed data from the International Severe Asthma Registry and Optimum Patient Care Research Database. †Study analyzed data from the Optimum Patient Care Research Database.
OCS: oral corticosteroid; IgE: immunoglobulin E; IL5: interleukin 5; IL5R: interleukin 5 receptor.

exacerbations, which is associated with accelerated lung function deterioration[7,46]. In a worldwide survey of severe asthma, including ISAR data, 51% of patients were receiving regular intermittent OCS, and fixed airway obstruction was prevalent; 44% worldwide had post-bronchodilator forced expiratory volume in 1 second/forced vital capacity <0.7[5], with even higher prevalence in the Asia-Pacific region[47]. Meanwhile, analysis of data from the United Kingdom (UK) Optimum Patient Care Research Database (OPCRD) has shown that asthma exacerbations accelerate lung function decline in adults, with a more pronounced association in younger patients[7]. An ISAR study found that the risks of severe exacerbations varied between patients with similar characteristics but who lived in different jurisdictions, suggesting the existence of unknown patient or health system factors[13]; hence, work is underway to develop a model to predict the risk of severe exacerbations patients with severe asthma, which could guide treatment escalation[14]. Data from Korean IASR patients and the Korean Chronic Obstructive Pulmonary Disease (COPD) Subgroup Study have shown similar prevalence of overlapping asthma/COPD (ACO) in patient groups with pure severe asthma or with pure COPD, with comparable lung function impairment and exacerbation risk in patients with ACO from either group[15].

2. Who, when, and how in treating severe asthma

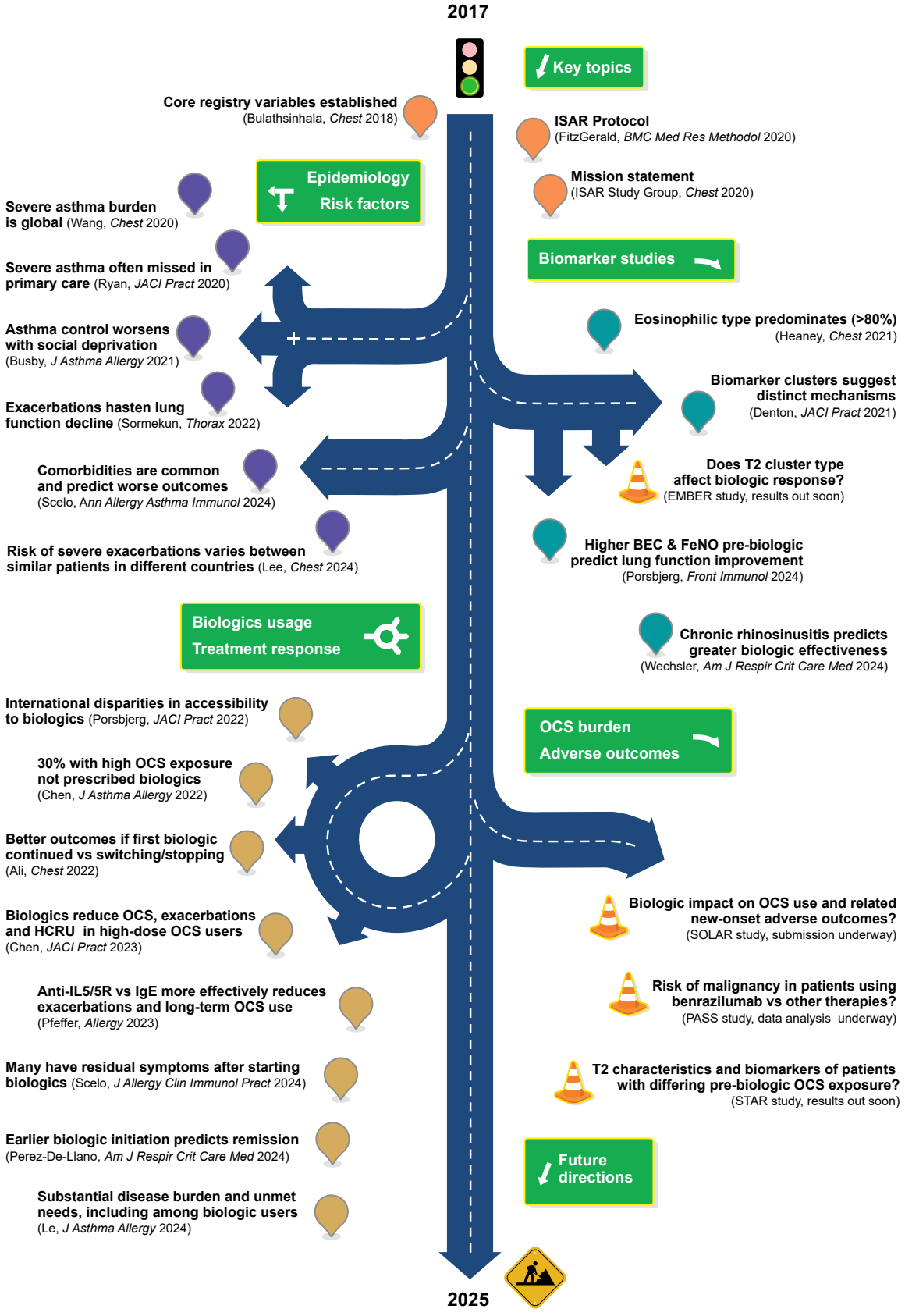
Minimizing systemic corticosteroid exposure is key to reducing damage to the body and lungs in patients with severe asthma[12,37,39,48]. Analysis of real-world data from ISAR is contributing to realizing this objective by identifying appropriate treatments for the right patients at the right time. A study of inflammatory biomarker expression revealed distinct clusters of patients that exhibited unique clinical characteristics, which suggests discrete patterns of underlying inflammatory pathway activation. Understanding how these mechanisms affect individual patients with severe asthma will help clinicians to target precision medicines, such as biologic therapies, to patients likely to benefit[8].

Characterization of severe asthma phenotypes in the ISAR population using an eosinophilic gradient algorithm, showed that most had type 2 inflammation[9], for which targeted treatments are available; accordingly, GINA has been recommending add-on biologic therapies for severe eosinophilic asthma since 2021[48,49]. Besides GINA, ISAR research has informed several other official guidelines; these include UK National Institute for Health and Care Excellence guidance on treating severe asthma with tezepelumab[50], management guidelines from Mexico[51] and Germany[52], and guidance on asthma care in older people[53].

Analyses of real-world patient data have also identified major barriers to specialist care for severe asthma. The earlier patients with severe asthma can be identified, the sooner they can receive appropriate treatment. Unfortunately, under-recognition of severe asthma in the primary care settings where patients with asthma are typically treated may be a barrier to referral for specialist care. A study of asthma patients from ISAR and the OPCRD estimated that although 8% of those managed long-term in primary care had potentially severe asthma, most (72%) had neither been referred nor received specialist care for more than a year despite being eligible[6]. Many patients with 'hidden' severe asthma may be managed with long-term OCS and lack access to specialist treatments, such as biologic therapies, with a more favorable risk/benefit ratio. Another OPCRD study showed that patients with asthma who were most socio-economically deprived had worse disease control and higher exacerbation rates compared with the least deprived, however, they were no more likely to be referred for specialist assessment and targeted treatments[11]. Registries such as ISAR and the OPCRD provide rich sources of real-world data that can be used to facilitate earlier identification of severe asthma in primary care and investigate the reasons for disparities in asthma management and how these could be addressed to improve patient outcomes.

The introduction of biologic asthma therapies has transformed the treatment landscape, and ISAR is providing valuable real-world data about the clinical applicability of biologics in patients with different characteristics and in different scenarios[31]. In an ISAR study that compared the effectiveness of initiating biologic therapies for severe asthma versus continuing long-term (≥1 year) or frequent rescue OCS (≥4 courses/year), both groups had improved outcomes at 1 year follow-up[21]. However, compared with ongoing OCS alone, biologic initiators had a significantly reduced exacerbation rate, were more likely to have a >50% reduction in OCS from baseline, and had lower risks of asthma-related emergency department visits and hospitalizations[21]. Similarly, in the ISAR CLEAR study, biologic initiators had a lower incidence of exacerbations during follow-up compared with non-initiators despite having more severe disease at baseline[54]. These results support the rationale for prescribing biologics, even in patients showing improvement on long-term or regular rescue OCS, as a potentially cost-effective strategy to further improve outcomes while minimizing OCS exposure[21]. The CLEAR study also highlighted the importance of timely initiation of the optimal biologic therapy; patients

Figure 3. International Severe Asthma Registry (ISAR) research journey and milestones, 2017 to 2024.
T2: type 2; BEC: blood eosinophil count; FeNO: fraction of exhaled nitric oxide; OCS: oral corticosteroids; HRCU: healthcare resource utilization; IL5: interleukin 5; IgE: immunoglobulin E. Road design adapted from PresentationGO (www.presentationgo.com).



with severe asthma who switched (25.5%) or stopped (14.5%) a biologic therapy, had higher rates of exacerbations and uncontrolled asthma than those who continued their initial biologic prescription; switchers also had a higher long-term OCS dose and more hospitalizations and emergency visits[18]. A study that compared the effectiveness of anti-immunoglobulin E (IgE) to anti-interleukin 5 (IL5) or anti-IL5 receptor (IL5R) in ISAR patients eligible for either biologic class found that, although both improved asthma outcomes, anti-IL5/5R was more effective in reducing exacerbations and long-term OCS exposure[19]. Nevertheless, if the response to an initial biologic is limited, clinicians may consider changing to another that might be more beneficial. Pertinently, ISAR research has revealed that switching is not common in current real-world practice; the SUNNIE study discovered consistently low rates of biologic switching worldwide, with only 11% of patients switching their initial treatment and 10% stopping[16]. Possible barriers to switching include the difficulty of getting an initial biologic prescription, which may put people off attempting to change to another, uncertainty about whether another biologic will improve upon marginal benefit from the first or may be ineffective, and limited evidence for benefits from switching. Hence, there is a need for further research into which patients respond best to different biologics[16]. Systemic barriers also limit the global availability and choice of different biologics for individualizing asthma treatment. An ISAR study highlighted substantial differences in national criteria for prescription and reimbursement of biologic asthma therapies, which result in marked variability in the accessibility of biologic agents between countries[17]. More than 60% of patients in the CLEAR study were not prescribed biologics despite meeting the eligibility criteria[54], and 30% of patients with high OCS exposure in GLITTER I did not receive biologics, despite a high rate of exacerbation comparable to that of biologics initiators[20]. Standardized prescription and access criteria are needed to overcome current barriers to wider availability and implementation of precision medicine for patients with severe asthma[17].

Other ISAR studies have continued to evaluate the effectiveness of both biologic and non-biologic asthma therapies in real-world clinical practice and to characterize factors that influence treatment responsiveness and outcomes in patients with severe asthma. For example, BEAM demonstrated that asthma control, exacerbations, and long-term OCS use can all be used to assess responsiveness to biologic therapies, which varied depending on the domain assessed and increased with worse baseline impairment, showing baseline status to be an important consideration in assessing treatment response[23]. PRISM II revealed that the presence of chronic rhinosinusitis, with or without nasal polyps, predicts greater effectiveness of biologic treatments for severe asthma[22]. Another study, FULL BEAM II, showed that clinical remission was more likely in patients with less severe asthma and shorter disease duration before biologic initiation; the odds of achieving four-domain clinical remission decreased by 15% for every additional 10 years asthma duration[26]. These findings support the rationale for early biologic treatment to achieve remission. Meanwhile, in the IGNITE study, higher baseline type 2 biomarkers (blood eosinophil count and exhaled nitric oxide) predicted improved lung function after initiating biologic therapy[24]. However, the EMBER study has highlighted the complexity of T2 inflammatory involvement in severe asthma and identified clusters of patients with varying biomarker elevations, including a predominantly female cluster with low T2 biomarker levels[10]. Importantly, other studies have shown that while patients who receive biologic therapies generally have better responses than those prescribed non-biologic treatments, a substantial proportion either do not meet clinical response criteria[25,27], or respond suboptimally, with persisting exacerbations, uncontrolled asthma, healthcare utilization, and long-term OCS use[25,28]. Further research is needed to understand how various factors may limit biologic responsiveness and to explore ways to optimize treatment[25]. One salient question is whether initiating biologics earlier may preempt irreversible lung damage and thereby improve patient outcomes[8,25,28].

Ongoing ISAR studies are investigating how differing OCS exposure before patients start biologic treatments affects the phenotype and biomarker profile of severe asthma (STAR), and how biologic initiation affects the burden of OCS and the subsequent onset of potentially OCS-related adverse outcomes (SOLAR). Another is exploring patterns of asthma onset and associated phenotypes (PATH), and a post-authorization safety study (PASS) is comparing the risks of malignancy between patients with severe asthma, who receive benralizumab, other biologics, or non-biologic therapies. Data analysis in these studies is underway and results will be published once available.

Data Collection and Quality Improvement Initiatives

QI—applying formal or informal tools to assess and enhance healthcare provision—is crucial to improving patient outcomes, which also benefits health services

and the economy[55]. However, while healthcare providers are increasingly embracing this concept, QI can be challenging to implement and incorporate into routine practice[55]. In collaboration with primary care clinicians, OPC has developed and refined automated QI programs that require modest resources and involve both clinic staff and patients, to promote a long-term culture of QI (Figure 4)[55].

ISAR's vision is to progress from changing clinical thinking via research to changing real-world practice through QI initiatives that improve both registry data quality and severe asthma care. Table 2 summarizes the ISC's ongoing QI agenda. The immediate goal is to improve the completeness and accuracy of data on specified ISAR core research variables (Supplementary Table S1). An important future goal is to minimize long-term (maintenance) use of systemic corticosteroids.

To these ends, ISAR rolled out two major QI initiatives in 2023–2024, a second Delphi exercise to refine the core ISAR research variables and improve the collection of high-quality data, based on 6 years of research experience, and an innovative QI program and data acquisition, processing, and reporting system—QISAR—which integrates data collection with clinical consultations and facilitates the assessment and review of patients with severe asthma.

1. Delphi exercise to refine ISAR research variables

Since ISAR first defined a standard set of core research variables, data completeness has improved measurably. Before 2017, fewer than half of patients who initiated biologics had pre-treatment and post-treatment data for at least one of four core outcome domains (exacerbation rate, lung function, asthma control, long-term OCS use)—by 2020, this had risen to nearly 60%. Nevertheless, there is scope to further improve the quality of data collected in routine clinical care and recorded in ISAR[56]; indeed, this is increasingly necessary given the introduction of composite outcome measures of response or remission that require high-quality data across multiple domains[57]. As the ISAR dataset matured over the years and has been applied in diverse analyses, it has become clearer which variables are the most important for conducting research to fill current knowledge gaps, and which others might either have limited utility or be more challenging to standardize and collect internationally. Consequently, the ISC conducted a second Delphi exercise in 2023–2024 to refine and reprioritize the set of variables collected and thereby ensure the highest possible data quality; a key goal was to identify a subset of research variables crucial to advancing the understanding of severe asthma and improving patient care.

The inaugural ISAR Delphi study in 2017 reached consensus on 95 initial core variables, with the expec-

Figure 4. International Severe Asthma Registry (ISAR) quality improvement model.
OCS: oral corticosteroid.

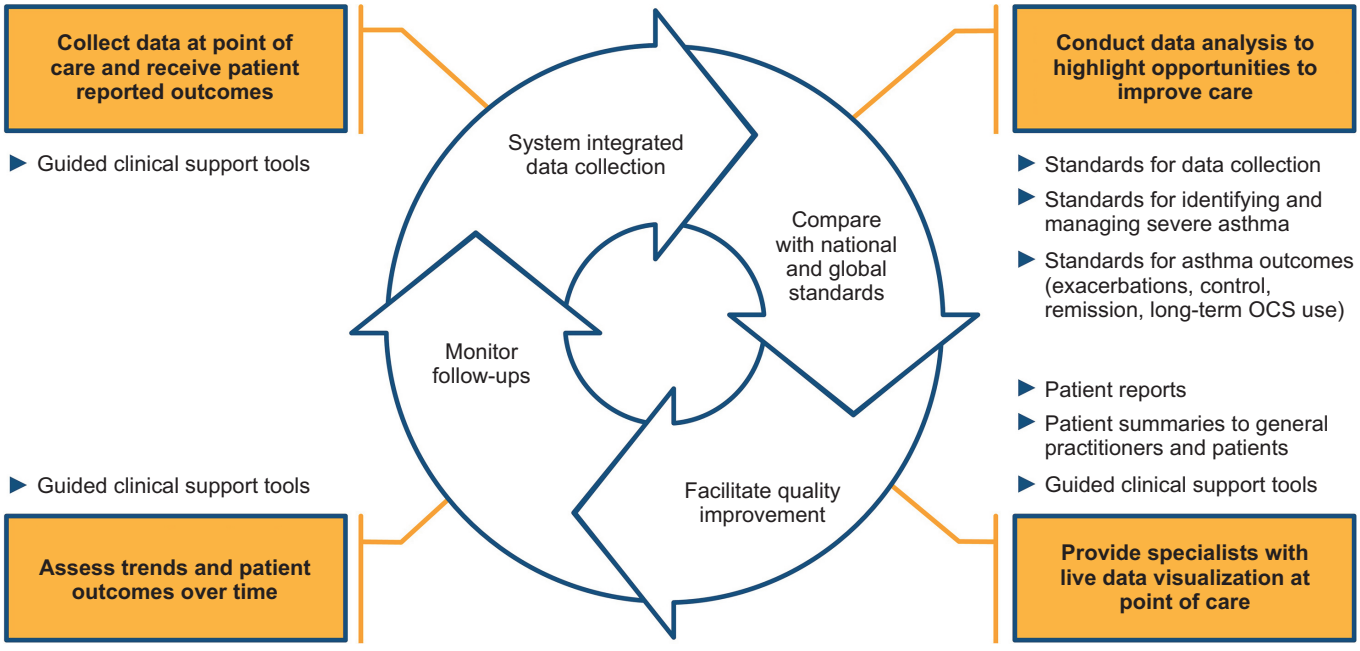


Table 2. International Severe Asthma Registry (ISAR) quality improvement agenda

Priority	Quality improvement goal	Timeframe
1	Collect 100% of key research variables* agreed by the 2024 Delphi exercise from all patients with severe asthma in long-term follow-up	2024 onward
2	Eliminate long-term (maintenance) use of systemic corticosteroids to treat severe asthma	2025 onward
3	Maximize achievement of clinical remission by patients with severe asthma†	Future goal
4	Improve the visualization of the longitudinal patient journey in severe asthma, focusing on core outcome measures‡	Future goal
5	Integrate asthma care pathways and management between primary and secondary care§, to expedite specialist management for patients with high-risk asthma, standardize care, and facilitate clinical trial recruitment.	Ongoing

*Participating ISAR centers undertake to collect 100% of key research variables and 90% of core variables, as defined by the ISAR 2023/24 Delphi exercise (Supplementary Table S1). †Both short-term, by using the best biologic for each patient, and long-term, by starting biologic treatment earlier. ‡Remission, long-term OCS use, exacerbations, lung-function, and asthma control. §Where health-care systems permit (i.e. electronic medical records exist, and primary care data are accessible).

tation that participating ISAR centers would achieve at least 90% collection and submission of these data to ISAR[3]. During the second, four-round, modified Delphi process in 2023, with a follow-up in 2024, ISAR experts considered approximately 150 potential variables, including the original 95 plus others in 'safety' and 'effectiveness' categories, and eliminated those below a pre-specified consensus threshold in successive rounds, eventually reducing the number to 73 individual core variables across 10 data categories. Thirty-three of these are designated 'key' variables, deemed essential for clinical research, and for which participating centers are contractually obliged to collect and upload data from 100% of patients. Supplementary Table S1 summarizes the core and key data fields to be completed and reported at the first visit for severe asthma and at subsequent visits. Other variables, including some dropped from the core variables list and others newly proposed, may still be collected but are designated optional, due either being considered to have limited utility or because they would be too challenging to standardize and collect by all centers under current local circumstances.

Several noteworthy changes were decided in finalizing the ISAR 2024 variables. Allergic rhinitis was designated 'core' rather than 'key' because, although associated with atopic asthma, it has been found not to be a relevant factor in responses to biologic therapies[22], which limits its utility as a research variable; some countries do not even collect data on allergic rhinitis. The background asthma therapy start-date and dates of key serum biomarker tests, including the highest blood eosinophil count, IgE count, and fractional exhaled nitric oxide (FeNO) test at follow-up, were upgraded from 'optional' to 'core' variables, as these are all considered important research metrics. The baseline FeNO test result remains a key variable despite being challenging for some centers to collect, for example due to limited reimbursement or equipment, or not being done routinely; however, centers unable to provide these data for 100% of patients will be accommodated. Highest education level was added as an optional variable to provide a proxy measure of socioeconomic status. Use of steroid-sparing agents can be an informative metric but was demoted to 'optional,' as these products are seldom used in the era of biologics. The variable 'Other factors contributing to severe asthma symptoms' and several tests, including chest computed tomography scan, PC20 methacholine/histamine challenge, and bone densitometry, were also changed from 'core' to 'optional' due to consensus that these data were of limited utility. Serum IgE and adherence remain 'key' and 'core' respectively at baseline but have been designated 'optional' at follow-up visits.

2. QISAR

Since its inception, ISAR has recognized that improving the quality of care in severe asthma requires research data collection to be integral to routine clinical care. Building on a QI model that OPC Australia developed to facilitate the assessment and review of patients with difficult-to-treat asthma, ISAR launched a new QI platform—QISAR—in 2024. QISAR integrates two main data processing systems: a clinical toolset, hosted on the REDCap platform[58], and a suite of interactive digital dashboards provided by OPC to ISAR members. These tools aim to harmonize research data collection with clinical consultations and to improve the provision of

evidence-based care.

The clinical tools include a new web-based clinical report form (CRF) inspired by the Denmark Severe Asthma Registry digital tool, a patient questionnaire designed to integrate seamlessly with the CRF, and automated instant clinical summary reports. These summaries can be integrated into electronic medical records to share with patients and primary care doctors, and can be extracted into a clinical letter template. This QI toolset minimizes duplicate data entry, automatically flags missing data, and was developed with input from clinical experts to make severe asthma consultations easier and more effective for both patients and clinicians.

All data, regardless of source, are processed centrally via the OPC database for visual output via a suite of interactive dashboard reports that enable longitudinal tracking of key outcomes, such as spirometry, long-term OCS use, exacerbations, and asthma control, at both individual patient and site/country levels. These interactive reports also provide evidence and data-based practice change suggestions, and account for variations between countries in control score type, biologic eligibility criteria, input language, medication trade names, and treatment guidelines.

Vision for the Future

The ISC convened at the 2023 European Respiratory Society Congress to set out their priorities for the future. ISAR envisions a world where: QISAR tools are used to collect standardized data during consultations and to track and optimize each patient's treatment journey; long-term systemic corticosteroid use is eliminated; asthma management is tailored to achieving clinical remission; timely specialist referral and initiation of biologic therapy are facilitated; and primary and secondary asthma care pathways and management are integrated to expedite specialist management of severe asthma and improve patient care and clinical trial recruitment. Embedding clinical trials into real-world practice will facilitate development of the best possible care in severe asthma.

ISAR State in the World

Over seven successful years, ISAR has become a preeminent resource for global research on severe asthma and its management in real-world clinical settings. ISAR successfully established the first global adult severe asthma registry, which uniquely allows multiple national and regional registries to pool standardized data to create a comprehensive central dataset with sufficient statistical power to answer key research questions. Operating on the principles of openness and inclusivity, ISAR has catalyzed the assembly of a global community with the shared goal of enhancing care for patients with severe asthma through high-quality research. Since 2017, ISAR has expanded to include 29 countries across five continents, and curated data on nearly 35,000 patients worldwide at time of writing. ISARs key strengths lie in its global reach and wealth of experience in data capture and management, coupled with a strong governance framework that supports robust and ethical scientific research. Building on these foundations, ISAR research has already made substantial contributions to progress in identifying the right patients, at the right time, for the right treatments, while ongoing QI initiatives will facilitate the management of patients in the right ways. Our overarching ongoing mission is to continue to contribute to improving global health, both by influencing guidelines and healthcare policy and practice, and through advocacy and stakeholder engagement to reduce inequalities and address unmet needs.

Ethics Statement

ISAR database is registered with the European Union Electronic Register of Post-Authorization studies (ENCEPP/DSPP/23720). ISAR has ethical approval from the Anonymised Data Ethics Protocols and Transparency committee (ADEPT0218). All data collection sites in the ISAR have obtained regulatory agreement in compliance with specific data transfer laws, country-specific legislation, and relevant ethical boards and organizations. This review paper did not involve procurement of patient data, and as such a study-specific data sharing agreement or ethics review was not applicable.

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Conflicts of Interest

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Supplementary Material

Supplementary material can be found in the journal homepage (http://www.e-trd.org).

Supplementary Table S1. International Severe Asthma Registry (ISAR) core variables and key research variables.

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