CHEST

International Severe Asthma Registry
Mission Statement

*The ISAR Study Group**

Regional and/or national severe asthma registries provide valuable country-specific information. However, they are often limited in scope within the broader definitions of severe asthma, have insufficient statistical power to answer many research questions, lack intraoperability to share lessons learned, and have fundamental differences in data collected, making cross comparisons difficult. What is missing is a worldwide registry which brings all severe asthma data together in a cohesive way, under a single umbrella, based on standardized data collection protocols, permitting data to be shared seamlessly. The International Severe Asthma Registry (ISAR; http://isaregistries.org/) is the first global adult severe asthma registry. It is a joint initiative where national registries (both newly created and preexisting) retain ownership of their own data but open their borders and share data with ISAR for ethically approved research purposes. Its strength comes from collection of patient-level, anonymous, longitudinal, real-life, standardized, high-quality data (using a core set of variables) from countries across the world, combined with organizational structure, database experience, inclusivity/openness, and clinical, academic, and database expertise. This gives ISAR sufficient statistical power to answer important research questions, sufficient data standardization to compare across countries and regions, and the structure and expertise necessary to ensure its continuance and the scientific integrity and clinical applicability of its research. ISAR offers a unique opportunity to implement existing knowledge, generate new knowledge, and identify the unknown, therefore promoting new research. The aim of this commentary is to fully describe how ISAR may improve our understanding of severe asthma. CHEST 2020; 157(4):805-814

KEY WORDS: ISAR; severe asthma

Optimum treatment of severe asthma represents a major unmet need. Although it affects a relatively small proportion of the asthma population (approximately 5%-10%), and even less (< 1%) for severe uncontrolled eosinophilic asthma,[1-4] it accounts for > 50% of the costs attributed to the disease.[5] Those with severe disease incur on average three times the asthma medication costs as those with persistent disease.[6] Despite improvement in outcomes, severe asthma is still a cause of mortality.[7] There is, therefore, an unmet need to characterize and classify these patients with a view to improve therapy and reduce costs on a global scale. The World Health Organization[8] describes

ABBREVIATIONS: ADEPT = Anonymized Data Ethics & Protocol Transparency; EDC = electronic data capture; ICS = inhaled corticosteroid; ISAR = International Severe Asthma Registry; ISC = ISAR Steering Committee; OPC = Optimum Patient Care Global; RCT = randomized controlled trial; REG = Respiratory Effectiveness Group

*Collaborators from The ISAR Study Group are listed in the Acknowledgments.

FUNDING/SUPPORT: ISAR is conducted by Optimum Patient Care Global (OPC) Limited, and cofunded by OPC Limited and AstraZeneca.

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DOI: https://doi.org/10.1016/j.chest.2019.10.051

severe asthma as "uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity." However, in clinical practice, other terms are often used such as difficult to treat, refractory, unresponsive or brittle, steroid-dependent, and treatment-resistant.[8-10] This language is reflected in the European Respiratory Society/American Thoracic Society Task Force[2] definition of severe disease as "asthma which requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy." Confirmation of good adherence to therapy, proper inhalation technique, appropriate management of exposures and comorbidities, and accurate patient education are further required to distinguish severe asthma from asthma that is uncontrolled because of other causes, such as poor adherence or comorbidities.[11,12]

Prevalence estimates of severe asthma vary widely from country to country (ranging from 3.6% in The Netherlands to 8.1% in Denmark),[13-16] a reflection of different definitions used and difficulties associated with obtaining reliable figures as a consequence of differences in access to health care. Reliability of the data is further confounded by the possibility that patients with severe asthma may be hidden because of a variety of factors including a patient's willingness to live with, or tolerate, their symptoms and lifestyle limitations,[17-19] an acceptance of the need for frequent courses of oral corticosteroids as usual rather than exceptional care, pressure on primary care providers not to refer to specialist clinics, and/or lack of awareness that the condition needs specialist attention and intensive therapy, as well as newer treatment options. Therefore, the true prevalence of severe asthma may be higher than that reported in the literature.

Many countries have developed regional and/or national severe asthma registries to gather information on severe asthma and to better understand the disease history, progression, impact, and response to treatment.[14,20-26] These registries have provided valuable information on country-specific epidemiologic patterns, risks, and treatment benefits, and have enabled safety monitoring of therapies. However, because of the relatively small size of the severe asthma population, and their spread over a wide geographic area,[2,3] such registries often have limited power to answer important research and clinical questions, and differ in their inclusion criteria and/or focus. Furthermore, because these registries were setup independently, it is hardly surprising that they reflect country-specific variability in patient selection, health-care access, and referral patterns and incorporate different data fields, ultimately collecting data of variable quality and completeness. This makes cross comparisons difficult and large-scale epidemiologic studies challenging. The discrete and segregated nature of these local registries means that there is no capacity for intraoperability with no linkage between them; therefore, valuable information is not shared in real time and cannot be contextualized within a global severe asthma framework until individual registry data are published.

What is missing is a worldwide registry which brings all severe asthma data together in a cohesive way, under a single umbrella. Pooling our resources to generate a centralized severe asthma dataset would permit data to be shared seamlessly between countries and institutions, to ultimately gain better insight into severe asthma on a global scale, covering response to therapies across all genetic backgrounds. This can be done by opening our severe asthma registry borders to share information gathered at the national and regional levels. The process may be further optimized by standardizing the variables collected, producing one overarching registry. The International Severe Asthma Registry (ISAR) (http://isaregistries.org/) is the first global adult severe asthma registry. It gathers patient-level, anonymized, longitudinal, real-life data from preexisting national registries (and newly established national registries, for which ISAR provides setup support) for adults with severe asthma, from countries all over the world. Severe asthma is defined by ISAR as those patients on Global Initiative for Asthma Step 5, or those with uncontrolled asthma on Global Initiative for Asthma Step 4.[27,28] Pooling data in this way provides important information for all stakeholders. With such a large dataset, physicians gain information not only on patient presentation, but also knowledge of predictors of treatment success in the era of personalized medicine and predicted outcomes of personalized therapies; patients gain a better understanding of the natural history of their disease, with their collective data used to inform treatment guidelines; payers get evidence on how treatments are used and their effectiveness (both clinical and economic) in different patient populations; and the pharmaceutical industry can assess the effectiveness and long-term safety of therapeutic agents in real life, fulfilling postmarketing surveillance commitments and identifying patients for future clinical trials.[29]

What Does ISAR Bring to Our Understanding of Severe Asthma?

ISAR contributes to our understanding of severe asthma in six key areas (Fig 1). It is the first global adult severe asthma registry, which ultimately will be large enough to ensure sufficient power to answer numerous important clinical questions. A pediatric registry is currently in the planning stages. The data collected by ISAR are standardized, individualized, and comprehensive. ISAR has scientific, academic, and ethical oversight providing confidence in data collection, analysis, and dissemination, and extensive experience in large data collection and management. It operates on the principle of inclusivity and collaboration, continually seeking new partners and prioritizing relevant research pertinent to severe asthma. Finally, ISAR is a cross-disciplinary initiative, holding within it the combined experience of key thought leaders in severe asthma (physicians and epidemiologists) and basic scientists, data analysts, and experts in database management and communication. Each of these six attributes contribute to ISAR's overall aim of improving the care of adults with severe asthma globally (both in primary and secondary care). This aim will be achieved via provision of a rich source of real-life data for scientific research to better understand the epidemiology, burden, clinical evolution, real-world safety of new treatment and management patterns of severe asthma (exploring differences across health-care systems), and to assess treatments (in the absence of comparative randomized controlled trials [RCTs]) and patient outcomes for severe asthma.

Global Reach

Patients with severe asthma are present over a wide geographic area. ISAR already partners with 20 national or regional registries in Europe (Bulgaria, Denmark, Greece, Ireland, Italy, Netherlands, Spain, and the United Kingdom), The Americas (United States, Canada, Columbia, and Mexico), Asia Pacific (Japan, India, South Korea, and Taiwan) and the Severe Asthma Web-based Database registry (comprising patient data from Australia, New Zealand, and Singapore), and the Middle East (Kuwait, United Arab Emirates, and Saudi Arabia), with planned expansion to other regions of the world—including Africa. Some of these local registries are currently being developed with ISAR involvement. At the time of writing this report, agreements were in process with eight countries (Finland, Germany, Iceland, Norway, Sweden, Singapore, Argentina, and Russia). Countries newly engaged include Portugal, Estonia, France, and Brazil, giving ISAR a truly global reach. ISAR currently comprises data from 7,948 patients with severe asthma (individual data: n = 7,250; aggregate data: n = 698), with new data provided quarterly. The

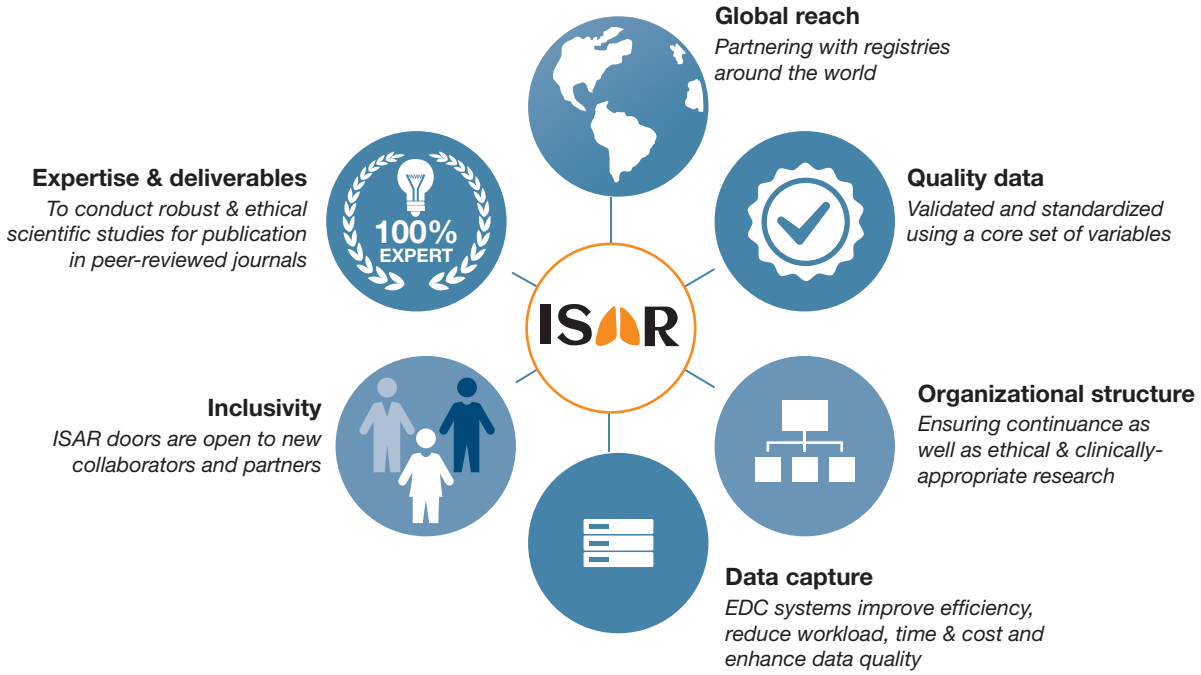

Figure 1 – *What the ISAR brings to our understanding of severe asthma. EDC = electronic data capture; ISAR = International Severe Asthma Registry.*

individual data are prospective for 2,113 patients and retrospective for 5,137 patients (Fig 2). ISAR is a joint initiative and would not exist without the data provided by local registries. Importantly, local registries retain ownership of their own data, but benefit from ISAR in terms of the analytic power it provides and cross comparisons with data from other countries. ISAR also supports setting up of local registries via provision of a standardized variables list and resource support in assessing data quality and/or an electronic data capturing system. The registry acts as a data custodian, collecting, collating, exploring, and analyzing standardized data provided by local registries. Countries participate by either enabling country data to be provided directly into ISAR or by allowing country data to be used for any research conducted under the ISAR initiative, and approved by ISAR's governance body.

Quality Data

The value of any global registry derives not only from its geographic scope and the data it collects, but also from the quality of that data. Data collected by ISAR is fully anonymized, and at individual rather than aggregate level, offering the potential to explore additional, more thorough, and appropriate analyses per research question compared with the limited options possible with aggregate data.[30] Patient-level data provide the opportunity to conduct biostatistical multivariate analyses to investigate the potential relationship between outcome and risk factors, and provide level of risk for a patient rather than for a group (eg, age group, country) to track patient progress longitudinally over the course of time and to analyze response to treatment and changes in medical management. ISAR's centralized analysis model also removes potential for discrepancies in the methodology of data analyses between countries, provides the ability to dig further into individual country data (as part of a multinational dataset), and is a cost-effective and time-efficient approach. Data collection is standardized across all ISAR-contributing countries, using a core set of variables which all participating countries have agreed to collect. Arriving at the final list of variables to collect involved in-depth analysis of key variables collected by other registries and formulation of a comprehensive list of those variables (747 in total) and a modified Delphi, consensus-driven approach to reduce this list to 95 core variables, all overseen by a panel of 27 experts from 16 countries in the field of severe asthma.[27] This final list of 95 core variables encompasses data on patient demographics, medical history and diagnostics (eg, peripheral blood and sputum eosinophil levels, neutrophil levels and fractional exhaled nitric oxide), clinical characteristics, patient-reported outcomes, and treatment management plans.[27] The core variable list may also be added to with optional standardized safety and effectiveness bolt-ons, capturing information on

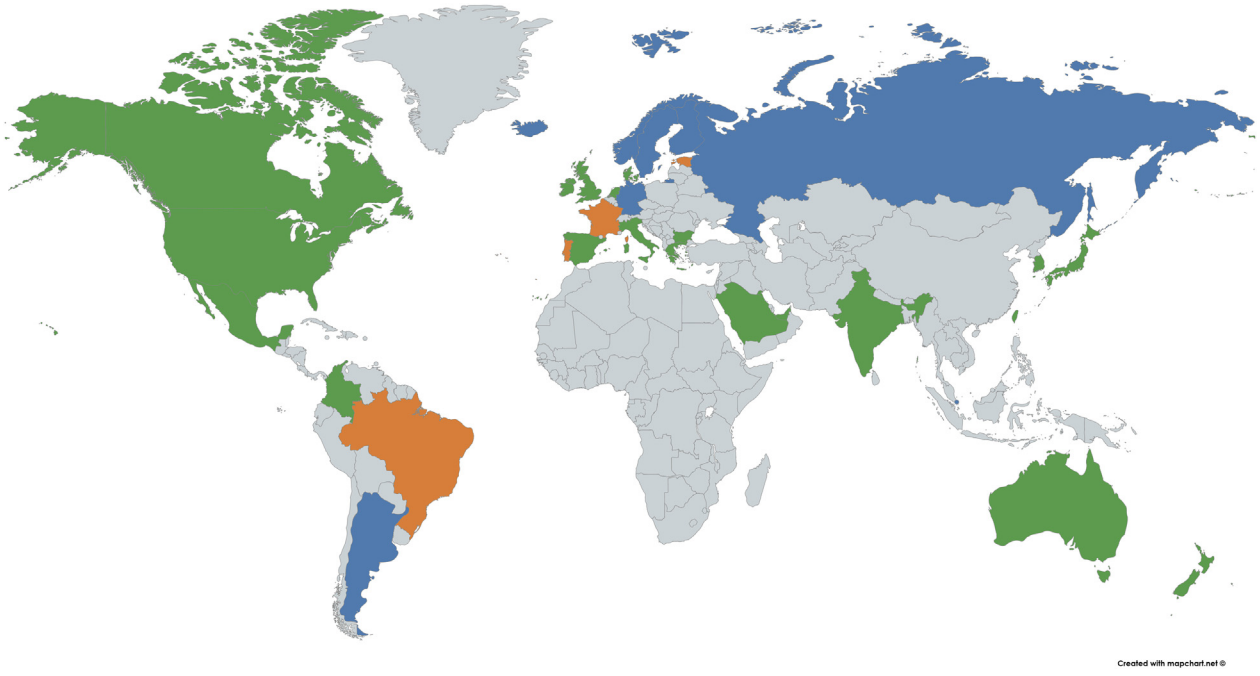

Figure 2 – *Global coverage of the ISAR. Green indicates the current contributors to ISAR, blue indicates the future contributors to ISAR, and orange indicates the countries engaged with ISAR. See Figure 1 legend for expansion of abbreviation.*

severe infection, malignancies, anaphylaxis, additional comorbidities, time of exacerbation, ICS/oral corticosteroid dose, and reasons for medication switching. Although the list is comprehensive, it is also reduced to the minimum necessary to reduce data input time and error, and to provide meaningful information on severe asthma in real life. This may help to define a link between best practices and improved outcomes and, at the same time, ensure the sustainability of ISAR moving forward.[27] Local registries are free to collect country-specific variables.

Organizational Structure

Currently, ISAR benefits from the support of three collaborators. It is overseen by four governing bodies safeguarding continuance of the registry into the future, and ensuring ISAR research is ethical, clinically appropriate, and continues to bring genuine value to patients, public health, and health care. ISAR is a registered data source on European Network of Centres for Pharmacoepidemiology and Pharmacovigilance asthma (http://www.encepp.eu/encepp/viewResource.htm?id=24389). The core collaborators currently include the following: Optimum Patient Care Global (OPC), the Respiratory Effectiveness Group (REG), and AstraZeneca. OPC is an organization which specializes in delivering medical research and services to improve the diagnosis, treatment, and care of chronic diseases. It has a long-standing record of delivering clinical support services and global research by developing enhanced quality databases and bespoke datasets for academic research and global registries with the aim of improving patient outcomes. REG is an investigator-led, not-for-profit research initiative, promoting the value of real-life research. ISAR's four governing bodies include the ISAR Steering Committee (ISC) (comprising 48 experts in severe asthma research from 29 countries and medical experts from AstraZeneca), REG, the Anonymized Data Ethics & Protocol Transparency (ADEPT) Committee, and the ISAR Operational Committee. The ADEPT Committee is commissioned by REG to review ISAR research protocols for their scientific quality and rigor. The ISAR Operational Committee includes participating country representatives (eg, country lead, deputy, data managers) and is involved in the day to day running of ISAR.

Data Capture

Electronic data capture (EDC) systems improve efficiency, reduce workload, time, and cost, and enhance the quality of data collected. ISAR data collection is supported by the use of a dedicated template, and also integrates with existing data capture systems (eg, OpenClinica, REDCap, other country-specific systems). These EDC systems ensure data quality via data validation and editing at the point of data entry. Automatic data validation rules are built into the EDC platforms to minimize errors at data entry. The data are secure and password-protected, and anonymized and encrypted at source. Mandatory variables must be entered, or a no data value imputed to confirm genuine missing data, maximizing registry completeness and minimizing bias. Furthermore, where possible, the ISAR data capture process has been streamlined to maximize efficiency. For example, patients may complete patient-reported outcomes remotely in the comfort of their homes or in the waiting room, and in certain countries (eg, Denmark) the ISAR data capture template has been embedded into electronic medical records, therefore avoiding double-entry as much as possible, reducing the administrative burden, and fulfilling a recent call for greater integration between routine health-care records, research databases, and biosamples.[31]

Inclusivity

ISAR operates under the principle of inclusivity and openness. The ISAR doors are open to new collaborators and partners using the Join Us or Register Interest functions on the ISAR home page. Research ideas may be suggested by ISC members, country leads, and contributors and visitors to the ISAR webpage (which includes third party commercial and academic research organizations) by simply clicking the Submit Proposal or Request Research tab. Each year all research ideas are reviewed, selected, assessed for scientific rigor and compliance with ethics standards, and prioritized by the ISC. Other academic and commercial entities can seek ISAR data access for research purposes, with all research proposals requiring approval by both the ISC and ADEPT.

Experience and Deliverables

ISAR holds within it the combined experience of 45 key thought leaders, bringing together the severe asthma knowledge from 29 countries. It benefits from the capability of the OPC database management team (which oversees one of the largest respiratory databases in the world [Optimum Patient Care Research Database]), ensuring the capture of high-quality data, management of the dataset, and robust and ethical scientific analyses. Finally, ISAR incorporates an experienced communications team committed to

ensuring timely dissemination of findings in international, peer-reviewed journals and international and regional scientific meetings.

In terms of deliverables, ISAR offers a unique opportunity to observe the real-life severe asthma situation and to assess the effectiveness, safety, and value of new therapeutic agents (and existing ones), providing valuable and complementary data to that obtained in the more rigid and homogenous RCT environment. ISAR is committed to producing a minimum of six datasets annually. Core projects already commissioned include a description of demographic and clinical characteristics of patients with severe asthma worldwide, and characterization of eosinophilic asthma vs noneosinophilic phenotype. Other prioritized research for the coming years is shown in Table 1. As may be expected in severe asthma, there is a strong research focus on biologics, but other topics are considered just as important such as assessing hidden severe asthma in primary care, the relationship between socioeconomic status and asthma outcomes, and characterization of health disparities across countries.

Limitations and Advantages of Registry Data

As an unavoidable consequence of their design, data obtained from registries possess lower internal validity than RCTs, limiting the extent to which they can demonstrate a cause-and-effect relationship. A major challenge is the bias inherent in its volume, knowing what to look for and how to assess and analyze large amounts of data.[32] Bias can be minimized by identifying eligible populations; by controlling the study design, study outcomes, and potential confounding factors (eg, missing data) before work commences; and by using rigorous analytic methods.[33] Additionally, a database is only as good as its data (ie, what is measured, in whom, how is it measured and recorded). A system to routinely validate and verify data integrity is essential to ensure database utility.[34] Because the patients included in ISAR are those from tertiary centers (rather than from primary care), we expect that they all have asthma. There is the possibility, however, that some patients may have asthma-COPD overlap. An ISAR prioritized research project aims to describe the extent of asthma-COPD overlap in this severe asthma population. Furthermore, although North, Central and South America, Europe and the Asia-Pacific region are well represented within ISAR, there are still gaps in the global cover (eg, Africa). We continue to reach out to countries in these regions with existing registries, and are committed to providing assistance to those countries wishing to set up their own registry. The ultimate aim is

TABLE 1] ISAR Global Core Projects and Prioritized Research

Description
Global core projects
Demographic and clinical baseline characteristics of patients with severe asthma worldwide
Characterization and comparison of eosinophilic and noneosinophilic phenotypes
Comparative effectiveness across severe asthma biologic classes (anti-IL-5 vs anti-IgE) in patients eligible for both modalities
Prioritized research
Hidden patients with severe asthma in primary care vs ISAR
Impact of exacerbation burden on lung function trajectory in a broad asthma population and severe asthma population
Biologics in severe asthma: utilization patterns, causes for discontinuation and switching, and adverse outcomes
Biomarker Relatability in the International Severe Asthma Registry
Identification of predictors (ie, biomarkers) of response to biologics
Hidden chronic asthma within the COPD/ACO population
Age at onset of asthma in patients with severe asthma
Relationship between socioeconomic status and asthma outcomes
Describe the OCS landscape: annual consumption, prevalence, outcomes, and side effects of long-term OCS users
Characterization of health disparities (burden of illness or mortality) across countries
Criteria for choosing and switching between similar biologic treatment options in patients with atopic and nonatopic severe eosinophilic asthma
Describe the characteristics of patients with severe asthma with inflammatory phenotypes and $FEV_1 < 40\%$

ACO = asthma-COPD overlap; ISAR = International Severe Asthma Registry; OCS = oral corticosteroid.

to make the ISAR software available open source to assist in the endeavor. Finally, merging data from preexisting registries brings its own challenges, including intercountry variability in the type of patients included in registries, referral patterns, and service access. Understanding the nature of each preexistent registry is important before drawing conclusions.

On the other hand, data entered into registries are not subjected to the same rigorous inclusion and exclusion criteria required for RCTs. This results in high patient numbers allowing comparisons between regions, countries, continents, and populations. Registries are population based and not subjected to the same sample size statistical limitations of RCTs. Registry data are also more heterogeneous in nature (than RCTs) and more representative of patients seeking medical advice in real life.[33] The data are not biased by changing patient/physician interaction, modification in health-care access, treatment(s) prescribed, or outcomes assessed in any way. An assessment of effect over a long period of time may also be better answered using registry data, which is precluded in RCTs because of cost. Registry data may be collected prospectively or retrospectively, and because these data are routinely collected, results can often be obtained more quickly and at a lower cost than RCTs.[33]

ISAR Vision and Conclusions

ISAR is a real-life registry with lower internal validity than clinical trial populations but extremely high external validity to the severe asthma population worldwide, as defined by the European Respiratory Society/American Thoracic Society criteria. It permits the implementation of existing knowledge in the severe asthma population, generation of new knowledge, and identification of the unknown, promoting new research. Because the severe asthma population is relatively small and heterogeneous, large numbers are needed to understand the complexities of cause, biological/clinical features, and outcomes, to provide personalized and targeted care. By combining data from small registries into one large standardized registry, comprising the same set of variables with similar data structures, we are able to compare and contrast differences between countries and care systems, something which is not currently possible in the global severe asthma framework. ISAR has the potential to robustly interpret and generally apply observations, but as it continues to grow, the aim is to no longer simply estimate, but rather to describe, the population in its entirety. ISAR's potential lies not so much in its ability to provide insight into asthma mechanisms, but rather in the information it provides for improving diagnosis, disease stratification (endotypes and phenotypes), and potentially the identification of new targets for treatment, an approach which is predictive, preventive, personalized, and participatory.[35] The challenge remains to harness ISAR's global data to provide meaningful clinical insight, and to translate this knowledge into better diagnosis and personalized care.[32] Generation of new knowledge will enable us to make the best choices for individual patients, providing the best treatment at the individual level (ie, the right treatment at the right time to the right patient), therefore making a meaningful and beneficial difference to the lives of patients with severe asthma around the world. By identifying the unknown, ISAR provides a fertile ground to do research to understand both the disease and the impact of current and new therapies.

Moving beyond ISAR, there is enormous potential to link ISAR with other databases (eg, with primary care data to find hidden severe asthma) to reduce the burden and cost of regularly scheduled visits in tertiary care centers, and to even link with other specialist databases/registries (eg, COPD) to gain further insight for patients with comorbidities. Data provided by ISAR may also be helpful in supporting, modifying, and improving current severe asthma guidelines. In the future, ISAR may be more fully linked with electronic health records to streamline data collection, and may also be linked with patient-reported outcomes, helping patients and physicians to make better personalized decisions. Knowledge gathered by ISAR from patients with severe asthma may be used to improve the management of those with moderate disease (eg, to ascertain whether better care earlier may lead to better outcomes later). The ISAR database could also be used to investigate the effectiveness of novel approaches to asthma treatment or indeed the feasibility of new asthma treatment paradigms. For example, the proposed paradigm of regular treatment with biologics (in those patients likely to respond), concomitant reduction of ICS dose, and use of dual or triple combination therapy as a reliever on an as-needed basis deserves investigation.[36] ISAR could be used not only to examine asthma outcomes and identify patients likely to benefit, but also to assess the cost-effectiveness of the approach. Potential benefits are many and include improved adherence and asthma control, fewer ICS-related side effects, and provision of a validated simplified asthma management program offering greater convenience for patients.[36]

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: G. W. C. has received research grants and lecture or advisory board fees from A. Menarini, Alk-Abello, Allergy Therapeutics, Anallergo, AstraZeneca, MedImmune, Boehringer Ingelheim, Chiesi Farmaceutici, Circassia, Danone, Faes, Genentech, Guidotti-Malesci, GlaxoSmithKline, Hal Allergy, Merck, MSD, Mundipharma, Novartis, Orion, Sanofi-Aventis, Sanofi, Genzyme/Regeneron, Stallergenes, UCB Pharma, Uriach Pharma, Teva, Thermo Fisher, and Valeas. M. A., T. N. T., and J. Z. are employees of AstraZeneca, a cofunder of the International Severe Asthma Registry. A. A. has received lecture fees Bayer, Boehringer Ingelheim, Berlin-Chemie Menarini, Chiesi, GlaxoSmithKline, MSD, Norameda, Novartis, and Orion; sponsorships from AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, GlaxoSmithKline, MSD, Norameda, Novartis, Roche, Teva and United Therapeutics; and research support from Bayer, CSL Behring, GlaxoSmithKline, Norameda, Pfizer, and Takeda; and has been a member of advisory boards for AstraZeneca, Boehringer Ingelheim, CSL Behring, GlaxoSmithKline, MSD, Novartis, Roche, Sanofi, Shire Pharmaceuticals, and Teva. E. B. has received lecture or advisory board fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi/Regeneron, and Teva; and research grants to her institution from AstraZeneca, GlaxoSmithKline, Novartis, and Teva. L. B. has received lecture or advisory board fees from Alk-Abello, Airsonett, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis and TEVA. U. B. Unnur Bjornsdottir receives gratuities for lectures/presentations from AstraZeneca, Sanofi and Novartis. A. B. has received speaker fees and grants to his institution from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and Novartis for unrelated projects. G. G. B. has received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, and Teva; and is a member of advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi/Regeneron, and Teva. B. G. C. declares grants from Chiesi; personal fees for advisory board activities from Chiesi and AstraZeneca; and payment for lectures/speaking engagements from Chiesi, Novartis, Menarini, and AstraZeneca, outside the submitted work. R. W. C. has received honoraria for lectures from Aerogen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Teva; is a member of advisory boards for GlaxoSmithKline and Novartis; has received grant support from GlaxoSmithKline and Aerogen; and has patents in the use of acoustics in the diagnosis of lung disease, assessment of adherence, and prediction of exacerbations. P. G. G. declares speaker fees and grants to his institution from AstraZeneca, GlaxoSmithKline, and Novartis for unrelated projects. L. G. H. is Academic Lead for the UK MRC Consortium for Stratified Medicine in Severe Asthma - Industrial Pharma partners Amgen, AstraZeneca, Medimmune, Janssen, Novartis, Roche / Genentech, GlaxoSmithKline, and Boehringer Ingelheim; prior project grant funding from Medimmune, Novartis UK, Roche / Genentech, and GlaxoSmithKline; has taken part in Advisory Boards / Lectures supported by Novartis, Roche / Evelo Biosciences, Genentech, GlaxoSmithKline, Teva, Theravance and Vectura; has travel funding support to international respiratory meetings (AstraZeneca, Chiesi, Novartis, Boehringer Ingelheim, Teva, and GlaxoSmithKline) and has taken part in asthma clinical trials (GlaxoSmithKline, Schering Plough, Synairgen, Novartis, and Roche / Genentech) for which his institution was remunerated. M. H. has received grants-in-aid, speaker fees, and fees for serving on the advisory boards of; GlaxoSmithKline, AstraZeneca, Novartis, Teva, and Sanofi, all unrelated to the current manuscript, and all paid to his institutional employer Alfred Health. E. H. participates in speaking activities and industry advisory committees for AstraZeneca, Sanofi-Genzyme, GSK, Novartis, TEVA, Circassia and Nestlè Purina. T. I. declares grants from Astellas, Boehringer Ingelheim, Daiichi-Sankyo, Kyorin, MeijiSeika Pharma, and Teijin Pharma; and declares lecture fees from Kyorin. R. C. J. declares grants from AstraZeneca, GlaxoSmithKline, and Novartis; and personal fees for consultancy, speakers fees, or travel support from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Nutricia, OPRI, and Pfizer. C. K. R. declares consultancy and lecture fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Mundipharma, MSD, Novartis, Sandoz, Takeda, and Teva-Handok. S. L. declares receipt of lecture (personal) and advisory board (to employer) fees from AstraZeneca, Boehringer Ingelheim, and Novartis. L. A. L. declares personal fees for consultancy and lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, Novartis, Orion Pharma, Sanofi and Teva; personal fees for consultancy from ALK; research grants for academic research on respiratory diseases from several Finnish foundations. A.-H. M.-Z. declares unrestricted grants from Boehringer Ingelheim, GlaxoSmithKline, and Novartis; personal fees for advisory board activities from AstraZeneca and Boehringer Ingelheim paid to Amsterdam UMC; travel grant from Chiesi. N. G. P. declares research support from Gerolymatos, Menarini, Nutricia, and Vian; and consultancy/speaker fees from ALK, ASIT, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, HAL Allergy, Menarini, MSD, Mylan, Novartis, Nutricia, and Sanofi. V. P. declares (in the last 3 years) honoraria for speaking at sponsored meetings from AstraZeneca, Chiesi, GlaxoSmithKline, and Novartis; travel grants from Chiesi and Novartis; consultancy fees from ALK, AstraZeneca, Boehringer Ingelheim, Mundipharma, and Sanofi; and funding/grant support for research projects from a variety of government agencies and not-for-profit foundations, and AstraZeneca, Chiesi, and Menarini. L. P. L. declares nonfinancial support, personal fees, and grants from Teva; nonfinancial support and personal fees from Boehringer Ingelheim, Esteve, GlaxoSmithKline, Mundipharma, and Novartis; personal fees and grants from AstraZeneca and Chiesi; personal fees from Sanofi; and nonfinancial support from Menairi, outside the submitted work. M. P. declares personal fees and nonfinancial support from AstraZeneca and GlaxoSmithKline. Y. T. declares honoraria from Kyorin Pharma and Teijin Pharma and research funding from Kyorin Pharma and Meiji Seika Pharma. E. W. has received advisory board fees from AstraZeneca. She has been an investigator on clinical trials sponsored by AstraZeneca, GlaxoSmithKline, Novartis, Teva, and National Institute of Allergy and Infectious Diseases (NIAID) for which her institution has received funding. L. B., V. A. C., I. C., N. E., N. H., and C. A. P. are employees of Optimum Patient Care Global, a cofunder of the International Severe Asthma Registry. T. L. L. declares educational grants from AstraZeneca, Bayer, Boehringer Ingelheim, Care Pharmaceuticals, GlaxoSmithKline, Mylan, Novartis, Mylan, and Teva. D. B. P. has board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals, Thermofisher; consultancy agreements with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Novartis, Pfizer, Teva Pharmaceuticals, Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Teva Pharmaceuticals, Theravance, UK National Health Service; payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma, Novartis; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Mundipharma, Mylan, Novartism, Thermofisher; funding for patient enrolment or completion of research from Novartis; stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); and is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme, and Health Technology. None declared (V. B., G. C. C., J. M. F., M. K. S., D. L., C. M. P., M. S., Y. S. C., and R. B. M.).

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Role of sponsors: OPC and AZ co-sponsor the ISAR initiative, but only members of the ISAR Steering Committee had a role in study design, collection and analysis of data and manuscript preparation.

Other contributions: The International Severe Asthma Registry is conducted by Optimum Patient Care Global Limited, and cofunded by Optimum Patient Care Global and AstraZeneca. The following individuals have contributed substantially to ISAR: Magdalena Alexandrova, PhD, Ted Popov, MD, PhD, Ztekomir Vodenicharov, MD, PhD, and Alexandrina Vodenicharova, PhD (Bulgaria); Stelios Loukides, MD (Greece); Concetta Sirena for the SANI Registry (Italy); Philip Bardin, PhD, Belinda Cochrane, MBBS, David Langton, MD, Peter Middleton, PhD, Paul Reynolds, PhD, and John Upham, PhD (Severe Asthma Web-based Database Registry, incorporating Australia, New Zealand, and Singapore); Rocío Díaz Campos, MD, Santiago Quirce, MD, PhD, Lorena Soto Retes, MD, and Andrea Trisan, MD (Spain); John Busby, PhD, David Jackson, PhD, and Paul Pffefer, PhD (United Kingdom); and Jennifer Brandorff, Margo Brown, Jessica Cummings, Christena Kolakowski, Seth Skelton, Michael Wechsler, MD, and Joy Zimmer (United States).

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