

Development of the International Severe Asthma Registry (ISAR): A Modified Delphi Study



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What is already known about this topic? All existing severe asthma registries in the world were either country or region specific. Most importantly, none shared a common set of variables for data collection. This impedes data sharing and subsequently disallows data pooling to conduct research with robust sample size.

What does this article add to our knowledge? This paper depicts a systematic method of soliciting group consensus on a topic that entails a spectrum of choices and viewpoints.

How does this study impact our current management guidelines? Using the standardized minimal list of variables identified by our study, we hope to achieve data interoperability between severe asthma registries across the globe and subsequently improve patient management guidelines in severe asthma.

BACKGROUND: The lack of centralized data on severe asthma has resulted in a scarcity of information about the disease and its management. The development of a common data collection tool for the International Severe Asthma Registry (ISAR) will enable

standardized data collection, subsequently enabling data interoperability.

OBJECTIVES: To create a standardized list of variables for the first international registry for severe asthma via expert consensus.

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This study is cofunded by Optimum Patient Care Global and AstraZeneca.

Conflicts of interest: L. Bulathsinhala, N. Eleangovan, V. Carter, C. Price, T. Le, and M. S. d'Alcontres are employees of Optimum Patient Care, a cofunder of the International Severe Asthma Registry. L. G. Heaney has taken part in advisory boards and given lectures at meetings supported by GlaxoSmithKline, Respivert, Merck Sharpe & Dohme, Nycomed, Boehringer Ingelheim, Teva Pharmaceuticals, Vectura, Novartis, and AstraZeneca. He declares sponsorship for attending international scientific meetings from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Napp Pharmaceuticals; and speaker fees from AstraZeneca, Aerocrine, Hoffman-La Roche, and Teva Pharmaceuticals. A. Menzies-Gow declares grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Hoffman La Roche; consultancy agreements with AstraZeneca and Vectura;

Abbreviation used

ATS- American Thoracic Society
BTS- British Thoracic Society
CRF- Case Report Form
ERS- European Respiratory Society
GINA- Global Initiative for Asthma
ICS- Inhaled corticosteroids
ISAR- International Severe Asthma Registry
ISC- ISAR Steering Committee
SAWD- Severe Asthma Web-based Database

METHODS: A modified Delphi process was used to reach consensus on a minimum set of variables to capture in ISAR: the core variables. The Delphi panel brought together 27 international experts in the field of severe asthma research. The process consisted of 3 iterative rounds. In each round, all Delphi panel members were issued an electronic ISAR Delphi workbook to complete and return to the ISAR Delphi administrator. Workbooks and result summaries were anonymously distributed by the Delphi administrator to all panel members at subsequent rounds. Finalization of the core variable list was facilitated by 2 face-to-face meetings.

personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hoffman La Roche, Napp Pharmaceuticals, Novartis, Teva Pharmaceuticals, and Vectura; nonfinancial support from AstraZeneca, Boehringer Ingelheim, and Napp Pharmaceuticals; and payment for travel expenses to international conferences from AstraZeneca, Boehringer Ingelheim, and Napp Pharmaceuticals. P. G. Gibson declares grants from AstraZeneca, GlaxoSmithKline, and Novartis; and personal fees from AstraZeneca and GlaxoSmithKline. M. Peters declares personal fees and nonfinancial support from AstraZeneca and GlaxoSmithKline. M. Hew declares grants and other advisory board fees from AstraZeneca, GlaxoSmithKline, Novartis, and Seqirus, with all payments to his institutional employer. L. Lehtimäki declares personal fees for consultancy and lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, Novartis, Orion Pharma, and Teva Pharmaceuticals; and personal fees for consultancy from ALK-Abelló. E. van Ganse declares grants from ALK-Abelló, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme; and personal fees from ALK-Abelló, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, IMS Health, and Merck Sharp & Dohme. L. P. de Llano declares grants from AstraZeneca, Chiesi, and Teva Pharmaceuticals; personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Esteve, GlaxoSmithKline, Mundipharma, Novartis, Sanofi, and Teva Pharmaceuticals; nonfinancial support from Boehringer Ingelheim, Esteve, GlaxoSmithKline, Menarini, Mundipharma, Novartis, and Teva Pharmaceuticals. A. H. Maitland-van der Zee declares unrestricted grants from GlaxoSmithKline and personal fees for advisory board activities from AstraZeneca. N. Papadopoulos declares personal fees for advisory board activities from BIOMAY, Faes Pharma, HAL Allergy Group, Novartis, and Nutricia Research; consultancy fees from MEDA, Menarini, and Novartis; institution grant from Menarini; personal fees for speaker/chairperson from Abbvie, Danone, MEDA, Merck Sharpe & Dohme, Novartis, and Omega Pharma. V. Backer declares collaboration, consultancy, unrestricted grants, and lecture fees from AstraZeneca, Teva Pharmaceuticals, Sanofi, Boehringer Ingelheim, GlaxoSmithKline, Merck Sharp & Dohme, Mundipharma, Novartis, and Sandoz; and is in the advisory board at AstraZeneca, GlaxoSmithKline, ALK-Abelló, Teva Pharmaceuticals, Sanofi, and Novartis. C. K. Rhee declares consultancy and lecture fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck Sharpe & Dohme, Mundipharma, Novartis, Sandoz, Takeda, and Teva-Handok. K. Verhamme works for a research group that in the past received unconditional research grants from Yamanouchi, Boehringer Ingelheim, Novartis, and GlaxoSmithKline. R. Buhl declares personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Novartis, Roche, and Teva Pharmaceuticals, as well as grants to Mainz University from Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Roche. B. G. Cosio declares grants from Chiesi;

RESULTS: Of the initial 747 selected variables, the Delphi panel reached a consensus on 95. The chosen variables will allow severe asthma to be assessed against patient demographics and medical history, patient-reported outcomes, diagnostic information, and clinical characteristics. Physician-reported outcomes such as nonadherence and information about treatment and management strategies will also be recorded.

CONCLUSIONS: This is the first global attempt to generate an ISAR using a common set of core variables to ensure that data collected across all participating countries are standardized. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:578-88)

Key words: Severe asthma; Disease registry; Delphi process

Asthma affects 5% to 15% of the population worldwide, and its prevalence has noticeably increased in recent decades.¹ This heterogeneous disease, characterized by variable symptoms including cough, wheeze, and dyspnoea, is associated with chronic airway inflammation. Management strategies, including asthma education, are aimed at achieving optimal disease control via minimization of current symptoms and prevention of acute exacerbations using a stepwise approach to medication.²

Although most patients with asthma have mild-to-moderate disease symptoms that may be well controlled with standard

personal fees for advisory board activities from Chiesi and AstraZeneca; and payment for lectures/speaking engagements from Chiesi, Novartis, Menarini, and AstraZeneca. G. Gopalan was formerly an employee of AstraZeneca. T. N. Tran is an employee of AstraZeneca, a cofounder of the International Severe Asthma Registry. D. Price declares board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, and Teva Pharmaceuticals; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, and Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp, Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Teva Pharmaceuticals, Theravance, UK National Health Service, and Zentiva (Sanofi Generics); payment for lectures/speaking engagements from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Merck, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme, Skyepharma, and Teva Pharmaceuticals; payment for manuscript preparation from Mundipharma and Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma and Novartis; payment for travel/accommodation/meeting expenses from Aerocrine, AstraZeneca, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; funding for patient enrolment or completion of research from Chiesi, Novartis, Teva Pharmaceuticals, and Zentiva (Sanofi Generics); stock/stock options from AKL Research and Development Ltd that 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 Assessment. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication April 17, 2018; revised July 30, 2018; accepted for publication August 13, 2018.

Available online September 1, 2018.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2018.08.016>

treatment, a smaller subpopulation remains uncontrolled and/or suffers from severe symptoms. The exact prevalence of severe asthma is uncertain but has been estimated at 5% to 10% of the asthma population.³⁻⁵ Such patients remain inadequately managed with the current standard of care,³ which includes high-dose inhaled corticosteroids (ICSs) with additional controllers and represents a significant unmet need.

There is compelling evidence to suggest that better standardized care for severe asthma is needed, including the registration of systematic assessment and improved and aligned registries of patients whose symptoms fulfill the criteria for severe asthma.⁶ Indeed, registries are well-established tools for tracking and reporting on the epidemiological attributes of a disease. They are valuable resources that enable treatment benefits and risks to be proactively monitored over time, through the collection of natural history data, and which aid the development of therapeutics and/or diagnostics. They can be used to gather information on disease progression and patient subgroups, facilitate patient recruitment into clinical trials, and generate real-world evidence on the safety and cost effectiveness of new therapeutics.⁷ Notably, registries are increasingly required as part of the postapproval safety monitoring process of regulatory bodies for new treatments.⁷

The current registry landscape for severe asthma is viewed as a collection of divergent, national and regional registries. The design, development, and maintenance of such registries has typically revolved around specific data collection platforms and drugs, leading to the creation of segregated systems with little or no collaboration between the different collections. Individual registries have limited power due to the relative rarity of severe asthma and stringent inclusion criteria. Different objectives and governance rules also exist across different countries and/or organizations. These disparities can lead to country-specific registries collecting different data fields of various qualities. These limitations lead to the implementation of only a subset of registry functions, resulting in the collection and analysis of limited data on severe asthma. Pooling data across multiple registries will improve the precision of incidence estimates, aid in identifying rare safety signals, and facilitate the exploration of possible drug-demographic, drug-disease, or drug-drug interactions in different subpopulations of the combined global severe asthma patients.⁸ To date, several national and regional severe asthma registries exist,⁹⁻¹² but none has an agreed international focus and standard list of data fields.

Using long-standing severe asthma registries from the United Kingdom⁹ and Australia,^{11,13} our aim was to gain expert consensus on a standardized list of variables on demographic, clinical characteristics, treatment, and comorbidities to establish the first international registry for severe asthma so that data can be seamlessly exchanged between countries and institutions without system-specific differences.

METHODS

This study used a modified, 3-round Delphi method process¹⁴ to select the common core variables to be collected in the International Severe Asthma Registry (ISAR). Variables were initially selected from previously existing national severe asthma registries. This helped to hasten the process of building the registry data collection framework by integrating real-world data elements that have been tested for feasibility of use and collection.

Panel selection

To achieve consensus, it was essential for the Delphi panel to include appropriately qualified and experienced individuals who could provide critical and discrete input toward the issue. The ISAR Delphi panel consisted of 27 experts in the field of severe asthma research. The panel members were invited from 16 different countries (Table E1, available in this article's Online Repository at www.jaci-inpractice.org), and were selected according to 2 or more of the following criteria:

1. Evidence of relevant asthma research published in high-ranking peer-reviewed journals (eg, high number of citations and research items).
2. A history of participation in the development and/or management of one or more severe asthma registries, epidemiological databases, and scientific congress committees in a particular country and/or internationally.
3. Experience as a medical provider with interest in advancing asthma management in clinical practice.

All the 22 ISAR Steering Committee (ISC) members were included in the list of 27 Delphi panel members, and hence, the Delphi panel was highly representative of the ISC. The 5 Delphi panel members not on the ISC were as follows: 1 pharmacoepidemiologist, 1 health-economist, 2 severe asthma clinical researchers, and 1 severe asthma database manager.

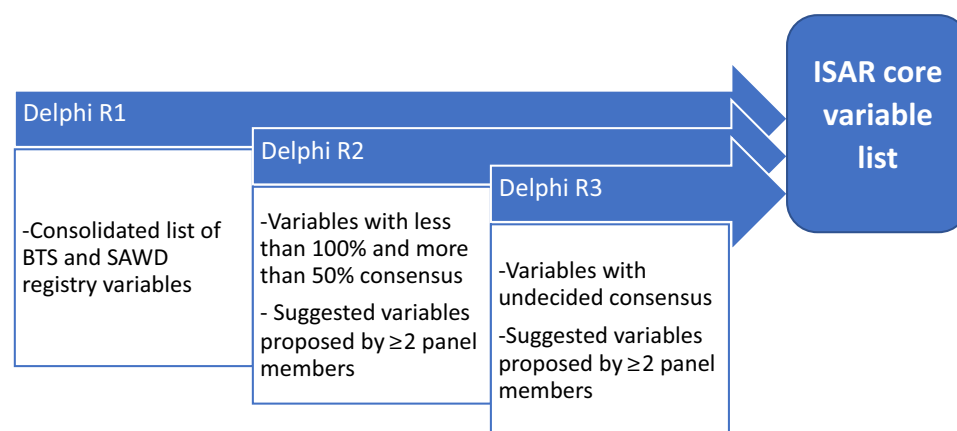
Modified Delphi process

A modified Delphi process was used to reach consensus.¹⁵ The process consisted of 3 iterative rounds (R1, R2, and R3) (Figure 1) where each Delphi panel member was issued an electronic ISAR Delphi workbook to review, provide suggestions, and vote to select core variables. Members then return the completed Delphi workbooks anonymously, to the ISAR Delphi administrator within a 2-week time frame stipulated for each round. The Delphi administrator directly corresponded with all panel members individually to ensure anonymity of replies and was responsible for disseminating a workbook and result summaries for each round.

Delphi R1. The Delphi workbook (*The ISAR Delphi Workbook Round 1*) was developed by consolidating the variable lists for the British Thoracic Society [BTS] Difficult Asthma Network⁹ and the Australian (Severe Asthma Web-based Database [SAWD])¹³ severe asthma registry. These variables were chosen as the initial bank of variables due to 15 years of usage and SAWD having the most number of variables amongst the existing severe asthma registries as of 2017. However, as there were 907 variables in both registries combined, and given that there are limited resources available for data collection, this exercise set out to determine not only the most appropriate variables but also to ensure that data collection for such variables can be sustained in a clinical setting.

Information from both registries was formally requested and extracted to develop 2 sets of variables: there were 115 variables in the "potential core" list (variables common to both registries; see Table I for a sample) and 632 variables in the "suggest" list (variables unique to either registry; see Table II for a sample).

The workbook was developed using Microsoft Excel 2016 MSO (V16.0) and consisted of a 2-tab spreadsheet with response-controlled questionnaires. On tab 1, displaying the potential core list (Table I), panel members were required to select an option ("Yes" or "No") via a drop-down menu for each variable, indicating whether they concur that the variable would be part of the ISAR core



BTS, British Thoracic Society; SAWD, Severe Asthma Web-based Database

FIGURE 1. General flow of the International Severe Asthma Registry (ISAR).

TABLE I. Sample of the “Potential Core” variable list from the International Severe Asthma Registry Delphi workbook Round 1

Page	Potential core variables	Field format	Response option (where applicable)	Unit (where applicable)	Place in core list?	Reason for choice (if “No”)
Patient details	Date of visit	Date		DDMMYY		
	Date of birth	Date		DDMMYY		
	Gender	Radio button	Female/Male			
	Ethnicity	Drop-down menu	Caucasian/South-East Asian/North-East Asian/African/Mixed/Other			
	Height	Decimal		M		
	Weight	Number		Kg		
	Bronchial thermoplasty	Radio button				

TABLE II. Sample of the “Suggest” variable list from the International Severe Asthma Registry Delphi workbook Round 1

Page	Suggest variables	Field format	Response option (where applicable)	Unit (where applicable)	Propose for core list?	Reason for choice (if “Yes”)
Sputum	Neutrophils	Decimal		%		
	Eosinophils	Decimal		%		
	Date of sputum	Date		DDMMYY		
	Sputum processing protocol	Text				
	Bronchial epithelial cells	Decimal		%		
	Bronchial epithelial cells	Decimal		109/L		
	Macrophages	Decimal		%		
	Lymphocytes	Decimal		%		
	Samples stored locally for biobanking	Radio button	No/Yes			

variable list. Panel members were also encouraged to nominate variables from the “suggest” variable list (Table II) on tab 2 and/or propose new variables. Experts were also encouraged to provide comments for excluding or including variables.

The Delphi workbook was sent to each Delphi panel member electronically, to be completed independently and returned via email to the Delphi administrator. At round closure, the Delphi administrator anonymized all returned workbooks and compiled all replies to tabulate frequency of responses, “Yes” and “No,” for each variable on the lists.

Variable consensus was then evaluated using summary statistics (frequency counts) generated with a statistical program (Stata 14; StataCorp LLC, College Station, Tex). Each “potential core” variable that received a majority (66.6%) or more consensus from the Delphi panel was selected as an ISAR core variable. However, with the first round of results, to exercise rigorous oversight, only variables with 100% consensus were added to the core list. Variables with less than 50% consensus were reviewed and removed. All other “potential core” variables were circulated for another round of review (Delphi R2). In tandem to the “potential core,” the “suggest” list of variables

was also reviewed to evaluate the number of votes by the Delphi panel. Variables with at least 2 “Yes” votes were then circulated for another round of review (Delphi R2). The Delphi R1 results were presented to the ISC (much of the Delphi panel consisted of ISC members [22/27]) during the inaugural ISC meeting in March 2017.

Delphi R2. As in R1, the expert panel was requested to engage in a similar voting process for Delphi R2 via a limited-response electronic questionnaire (*The ISAR Delphi Workbook Round 2*). The Delphi R1 summary results and panel member comments (“Reasons”) were anonymized and provided in the R2 workbook to facilitate an informed decision. Moreover, “Additional Information” on the use or functionality of these variables in the ISAR was provided to aid panel members in their decision. “Potential core” variables with less than 100% and greater than 50% consensus from R1 were included in the R2 workbook. In addition, “suggest” variables with at least 2 or more votes by Delphi panel members were disseminated for a full panel poll in R2.

Delphi R3. The Delphi panel also took part in R3 via a limited-response electronic questionnaire (*The ISAR Delphi Workbook Round 3*). “Suggest” variables and “potential core” variables were vetted concurrently in the same manner in R3, after finalization of “suggest” variables during R3 discussions by the Delphi panel. “Suggest” variables from R2 that had attained more than 50% consensus and “potential core” variables from R2 on which a consensus was not reached (>50% and <66.6% consensus) were circulated for another round (R3). In addition, because of high reliability, 9 of the “suggest” variables from R2 were consolidated into 4 variables/questions after discussion at the inaugural Steering Committee meeting. These were current occupation, age at start of asthma symptoms, environmental allergen test conducted, and current clinical management plan. These variables were added to the R3 workbook to ensure full vetting and review by the panel.

The ISAR core variables were finalized during the second ISAR Steering Committee Research Prioritisation meeting in May 2017. R3 results and all outstanding concerns raised by panel members, such as data field options for variables including ethnicity and occupation, were discussed and resolved. The participants were requested to re-evaluate the remaining 5 undecided variables to arrive at a consensus on which variables would be submitted for another Delphi round and, hence, which would be retained or removed from the final ISAR core variable list. The discussion was mediated by the Delphi neutral facilitator, who closed the gap of consensus by reminding the Steering Committee and/or Delphi members of the aim of the ISAR and the international study population under consideration. The final core variable list was shared with the Delphi panel in a Case Report Form (CRF). All chosen core variables were represented in the final CRF questionnaire format.

All variables that were not selected for the core list at the end of the Delphi process were compiled into a separate list. This list later gave rise to standard bolt-on variables, named “research variables.” “Research variables” are available to be adopted by a participating country-specific registry according to local research interests and capacity to collect and store data. A participating country is encouraged to add variables outside the core list to the country-specific registry, including and/or beyond the “research variable” list. All the “research variables” are available via Mendeley Data (<https://doi.org/10.17632/2zg9v6krbb.1>).

Data sharing

For the 3 types of variable lists shown below, the corresponding variable name and the related metadata, such as format and response options, are demonstrated in the “ISAR Delphi Process Variables Workbook”:

1. Sheet 1: matched “potential core” variables (List of matching variables from the BTS and SAWD registries)
2. Sheet 2: unmatched “suggest” variables (List of nonmatching variables from the BTS and SAWD registries)
3. Sheet 3: variables disqualified (List of variables removed from the total number of matching and nonmatching variables)

These data have been deposited into a secure electronic repository via Mendeley Data (<https://doi.org/10.17632/xdrdy37tbn.3>).

RESULTS

Delphi R1

Of the 27 members of the panel, 15 (55.6%) participated in Delphi R1; 28 of 115 initial “potential core” variables achieved complete consensus with 100% agreement for inclusion into the ISAR core variable list. Eighty of the remaining variables received greater than 66.6% and less than 100% consensus, 6 were undecided (50% to 66.6%), and 1 variable did not achieve consensus (<50%) (Table E2, available in this article’s Online Repository at www.jaci-inpractice.org). A total of 86 “potential core” variables (less than complete consensus [80] and undecided [6] variables) were fed into the second round of the Delphi process.

In addition, 54 “suggest” variables had attained at least 2 or more votes by the Delphi panel and moved on to the second round of the Delphi process (R2) (Table E2, available in this article’s Online Repository at www.jaci-inpractice.org). The remaining 578 “suggest” variables were then appropriately reviewed and removed from the Delphi process.

“Potential core” variables with undecided consensus were the GINA (Global Initiative for Asthma) Assessment for Asthma Control and patient status as a research subject. The asthma medication question regarding antileukotriene level received less than 50% consensus and was removed from the ISAR “potential core” variable list and the Delphi review process after assessment by the Delphi neutral facilitator.

Delphi R2

Thirteen panel members participated in R2 (48%). Eighty-six (less than complete consensus [80] and undecided [6] variables) “potential core” variables were considered in R2. Of them, 74 achieved consensus with more than 66.6% agreement for inclusion into the ISAR core variable list. Of the remaining variables, 8 were undecided and 4 did not achieve consensus. In addition, 9 of 54 variables in the “suggest” variable list attained more than 66.6% agreement for inclusion into the ISAR core variable list (Table E3, available in this article’s Online Repository at www.jaci-inpractice.org).

Of the 8 undecided variables, comorbidities (Ischaemic Heart Disease and Heart Failure), asthma medication (ICS, long-acting β -agonist, long-acting muscarinic antagonist), and allergen testing details were included in Delphi R3. As suggested by Delphi panel members, the probing order for the variable “Was blood eosinophil count collected during an exacerbation event?” was changed to a branch question versus a stand-alone question

and added to the core variable list after a thorough review by the neutral facilitator.

Variables without consensus were patient involvement in research trials, use of a nebulizer, short-acting β -agonists, and experience of adverse events. After further review by the Delphi neutral facilitator, these variables were removed from the core variable list.

Results from R2 were presented and discussed at the inaugural Steering Committee meeting in March 2017. The GINA Assessment for Asthma Control was chosen as the patient-reported measure of asthma control, and therefore, included in the core variable list. Because of highly related variables, the 9 newly indicated “suggest” variables were consolidated into 4 variables after detailed discussion and review among the Delphi panel. Altogether, 8 undecided “potential core” variables and the 4 consolidated “suggest” variables were included into R3 of the Delphi process.

Delphi R3

Fourteen Delphi members participated in R3 (51.9%). Four of 12 R3 “potential core” variables achieved consensus with more than 66.6% agreement for inclusion into the ISAR core variable list (Table E4, available in this article’s Online Repository at www.jaci-inpractice.org). Of the remaining 8 variables, 5 were undecided and 3 did not achieve consensus. On review by the Delphi neutral facilitator, and a face-to-face discussion with the Steering Committee in May 2017, 1 undecided variable was included into the core variable list. All 3 nonconsensus variables and remaining 4 undecided variables were removed from the core list. R3 resulted in 5 variables added to the core variable list. With all “potential core” variables achieving a status of consensus or nonconsensus, the Delphi exercise ended at R3.

To further streamline the process, undecided variables and nonconsensus variables such as asthma medication devices, prior clinical management plan, adverse events, and comorbidities (Ischaemic Heart Disease and Heart Failure) were removed from the core variable list. Date of bone densitometry was added to the core list after ISC discussion, despite the undecided status.

During the conclusion of R3 at the second ISC meeting in May 2017, a majority of the Delphi panel, all steering committee members (22 of 27), and the Delphi neutral facilitator agreed that ISAR should include 2 broad categories of patients similar to the European Respiratory Society (ERS)/American Thoracic Society (ATS) Task Force’s definition of severe asthma: patients receiving GINA Step 5 treatment, and patients with uncontrolled asthma at some point while receiving GINA Step 4 treatments.³ Patients considered to have uncontrolled asthma were defined as those having severe asthma symptoms, consisting of poor symptom control, airflow limitation, or serious exacerbations as per the ERS/ATS guidelines, or suffering exacerbations requiring 2 or more courses of oral corticosteroids.

The overall results from the Delphi process are summarized in Figure 2.

Final ISAR core variable list

The core variables that achieved consensus via the closely guided 3 rounds of Delphi were included in the final core variable list (Table III). The final ISAR core variable list consists of 95 variables, 83 variables that require data entry and 12 variables that do not require data entry (autopopulated). These variables are classified into 13 variable categories.

The core variables were reported in a CRF, which allowed a probing mechanism to take place with a branched questionnaire. A CRF was constructed to facilitate the process of data collection with enhanced clarity.

DISCUSSION

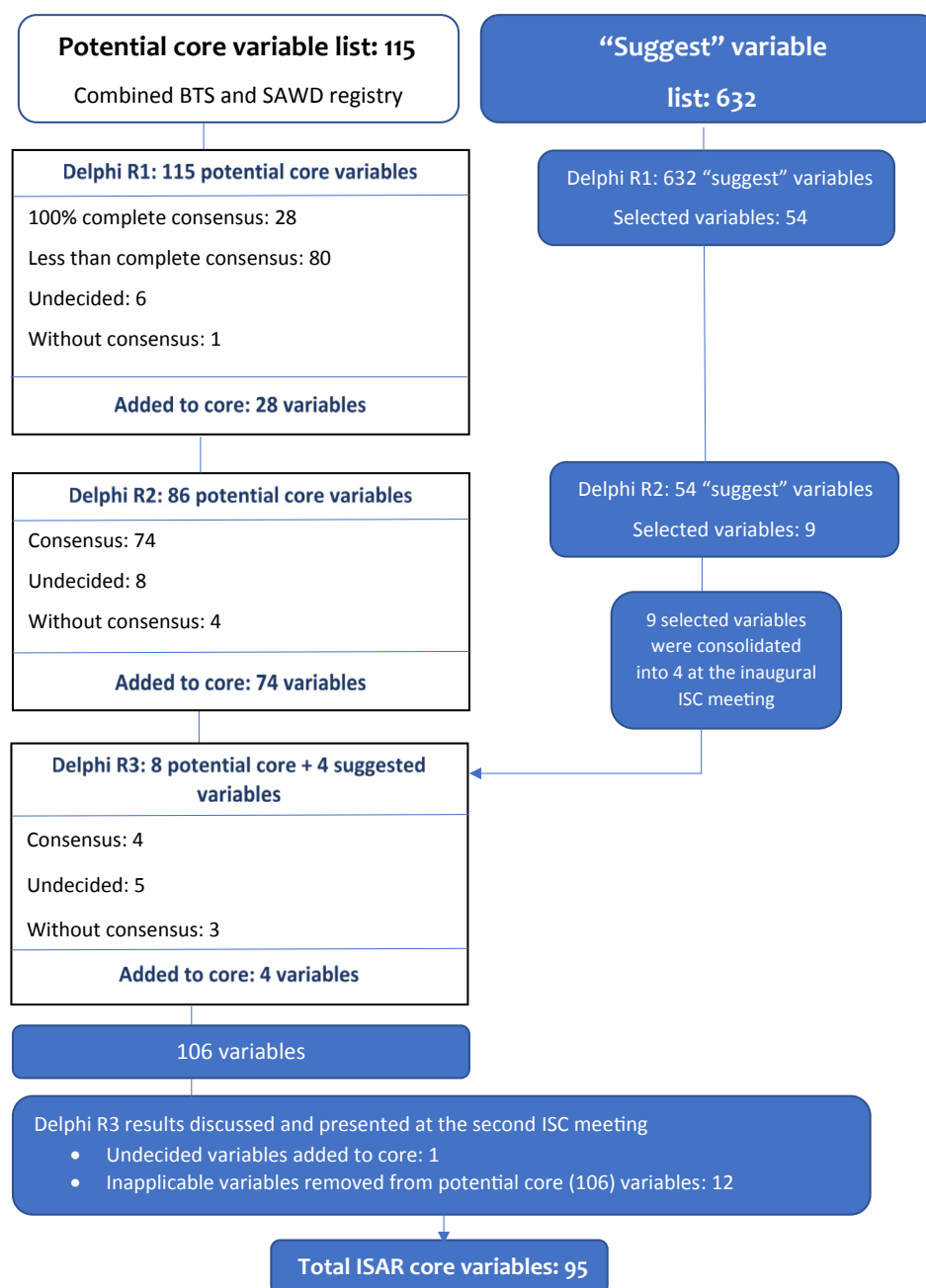
The aim of this Delphi-based study was to reach consensus among specialists in the field of severe asthma on a core set of data fields to include in the ISAR. Using the knowledge and experience of an international panel of severe asthma experts, workable criteria for registry purposes, a core set of variables, and a potential method to unify data for severe asthma from across the globe were generated. Analyses of these registry data will facilitate insight into this heterogeneous disease on a global scale. All potential variables underwent a rigorous, stepwise consensus process to ensure the collection of the minimum required information to effectively study the development, therapeutics, and management of patients with severe asthma.

Definitions, such as severe asthma, were based on expert opinion and precedence of use, because achieving consensus of what constituted severe asthma at an early stage in the process was important. The inclusion criteria, patients on GINA Step 5 therapy or uncontrolled on Step 4 therapy, were agreed upon by a majority of the panel to ensure the inclusion of patients with severe asthma in a real-world setting. These criteria served the primary purpose of the registry to prospectively survey patients with severe asthma. In addition, the inclusion criteria allowed the core data to be used for broader purposes (eg, uncontrolled asthma, etc.). The ISAR is not intended to assess the validity of real-life clinical practice, but merely to observe the evolving patterns of clinical care to ultimately evaluate its safety and/or effectiveness to improve the lives of patients. As such, no confirmation of asthma is required for enrolled subjects.

Of the initially circulated “potential core” and “suggest” variables, 95 variables achieved Delphi panel consensus. These variables represented 13 categories pertaining to the assessment and treatment of patients with severe asthma. Each category will serve to collect subsets of information essential for a more complete understanding of the disease. The successful limitation of core variables to less than 100 has resulted in an applicable CRF with a relatively small data entry burden for health care professionals who are participating in the registry. The specific domains that will enhance global registry recruitment and utility are discussed below.

Patient details and medical history

Patient demographic and medical history data fields will allow patients to be categorized.¹⁷ The panel-approved variables were chosen to ensure that a comprehensive set of patient characteristics are collected for patient aggregation. Previous studies have shown that many patients overestimate their level of asthma control and underestimate the severity of their condition, indicating that they tolerate symptoms and lifestyle limitations.¹⁸⁻²⁰ The GINA Assessment for Asthma Control was the preferred tool for this assessment, because previous studies have shown that it does not overestimate the proportion of patients with controlled asthma and is therefore more likely to give a less exaggerated score compared with other available questionnaires.²¹



BTS, British Thoracic Society; ISC, ISAR Steering Committee; SAWD, Severe Asthma Web-based Database

FIGURE 2. Summary of Delphi results for the International Severe Asthma Registry (ISAR).

Diagnostics

The expert panel agreed to collect screening and diagnostic results to help identify the care requirements of individual patients. Biomarkers such as peripheral blood and sputum eosinophils, and fractional exhaled nitric oxide have been shown to be useful for the management of asthma,^{22,23} and may help identify specific subtypes of severe asthma likely to benefit from treatment with novel biological agents.

Adherence and comorbidities

Nonadherence to therapy is approximately 50% in adults with severe asthma.²⁴⁻²⁶ Physicians need to ensure that patients are satisfied with their medication to increase adherence and optimize disease control.²⁷ The potential for ISAR to investigate nonadherence across different geographical regions, with likely different health care systems, availability of medications, and access to specialists and asthma education, was noted.

TABLE III. Final core variable list

Category	Variable field name
Inclusion criteria	(1) Receiving GINA Step 5 therapy (2) Uncontrolled receiving GINA Step 4 (ERS/ATS Guidelines) therapy: • Having severe asthma symptoms including poor symptom control, airflow limitation, and serious exacerbations • Frequent severe asthma exacerbations requiring systemic corticosteroids Patient fulfills the inclusion criteria for ISAR
Patient details	Date of visit Date of birth Age at assessment Gender Ethnicity Body surface area Body mass index Height Weight Bronchial thermoplasty
Occupation	Current occupation of the patient
Medical history	Current smoking status of patient Pack years • Number of cigarettes smoked per day • Number of smoking years Years since smoked Age at which asthma symptom began Number of exacerbations requiring rescue steroids in the past 12 mo Number of episodes of invasive ventilation ever Number of A&E attendances for asthma in the past 12 mo Number of hospital admissions for asthma in the past 12 mo
Comorbidity	Eczema Allergic rhinitis Chronic rhinosinusitis Nasal polyps Atopic disease (atopic dermatitis and allergic rhinitis)
Blood/sputum	Highest blood eosinophil count within the past year Date of highest blood eosinophil count within the past year Was this highest blood eosinophil count during an exacerbation event Highest blood eosinophil count within the past year and not during exacerbation Date of highest blood eosinophil count within the past year and not during exacerbation Current blood eosinophil count Date of current blood eosinophil count Highest sputum eosinophil count within the past year Date of highest sputum eosinophil count within the past year IgE count Date of IgE count
Diagnostics	Chest CT scan Date of chest CT scan Bone densitometry (DEXA) Date of bone densitometry (DEXA)
Lung function	Prebronchodilator FEV ₁ Postbronchodilator FEV ₁ Prebronchodilator FVC Postbronchodilator FVC Predicted FEV ₁ Prebronchodilator FEV ₁ (% predicted) Postbronchodilator FEV ₁ (% predicted) Predicted FVC Prebronchodilator FVC (% predicted) Postbronchodilator FVC (% predicted) FEV ₁ /FVC ratio prebronchodilator (%) FEV ₁ /FVC ratio postbronchodilator (%) PC ₂₀ methacholine/histamine test Date of PC ₂₀ test PC ₂₀ test result Fractional exhaled nitric oxide (FENO) test Date of FENO test FENO test result

(continued)

TABLE III. (Continued)

Category	Variable field name
Allergen testing	Environmental allergen test Serum allergy test: positive to allergen Serum allergy test: specify positive allergen and result Serum allergy test: date Skin prick test: positive to allergen Skin prick test: specify positive allergen and result Skin prick test: date
Asthma control	GINA Asthma Control Questionnaire In the past 4 wk, did the patient have: • Daytime symptoms more than twice per week • Any activity limitation • Any nocturnal symptoms/awakening • Reliever medication use more than twice per week • Lung function (PEF or FEV₁) <80% of predicted or personal best
Asthma medication	Maintenance oral corticosteroids Start date of oral corticosteroids ICS+LABA combination therapy Start date of ICS+LABA combination therapy ICS (only) Start date of ICS (only) therapy LABA (only) Start date of LABA (only) therapy LAMA Start date of LAMA therapy Theophyllines Start date of theophylline therapy Leukotriene receptor antagonist (LTRA) Start date of LTRA therapy Anti-IgE treatment Start date of anti-IgE therapy Anti-IL-5 treatment Start date of anti-IL5 therapy Macrolide antibiotic treatment Start date of macrolide antibiotic therapy Other steroid sparing agents
Adherence	Evidence of poor adherence*
Management plan	Other factors contributing to severe asthma symptoms [†] Current Clinical Management Plan [‡]

A&E, Accident & emergency; ATS, American Thoracic Society; CT, computerized tomography; DEXA, Dual Energy X-ray Absorptiometry; ERS, European Respiratory Society; FEV₁, forced expiratory flow in 1 s; FVC, forced vital capacity; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; ISAR, International Severe Asthma Registry; LABA, long-acting β -agonists; LAMA, long-acting muscarinic antagonist; PC₂₀, concentration of methacholine/histamine needed to produce a 20% decrease in FEV₁; PEF, peak expiratory flow.

*"Evidence of poor adherence":

This variable has the response options: "No," "Yes: subjective measure," and "Yes: objective measure"

Poor adherence to treatment can be indicated by selecting either (a) or (b):

- Subjective measure (eg, clinical impression, self-ending): opinion of a medical personnel for poor adherence to asthma medication therapy or patient self-report
 - For example¹⁶
 - Impression of "nonpersistence": patient stops taking medication
 - Impression of "nonimplementation": patient does not take medication as prescribed
- Objective measure (eg, prescription records, electronic monitoring): evidenced by medical records detailing asthma medication prescriptions being issued and inadequately filled or electronic monitoring obtained by smart inhalers patterns.
 - For example:
 - Medication possession ratio (MPR) = (sum of days' supply for all fills/number of days) $\times$ 100% <80% threshold.

[†]"Other factors contributing to severe asthma symptoms":

This variable calls for a trained clinician's perception or opinion on any other external factors (if any) that could contribute to the severe asthma symptoms of the patient

- For example:
 - Weather (cold air)
 - Air pollution
 - Physical activity (exercise-induced asthma symptoms)
 - Occupational triggers (workplace irritants, gases, chemical fumes, dust)

V. Strong smells (perfumes)

VI. Prior respiratory infections.

‡“Current Clinical Management Plan”:

This variable aims to record the asthma action plan for a patient to review efficacy over time

- For example:
 - I. Entry into clinical trial
 - If the patient is deemed suitable to benefit from a clinical trial drug
 - II. Discharge to local asthma service
 - If the patient has shown alleviated asthma symptoms
 - III. Optimization of current asthma therapy
 - If the patient’s current asthma therapy is titrated for better asthma management
 - IV. Bronchial thermoplasty
 - If the patient is eligible to have a bronchial thermoplasty surgery to manage their asthma
 - V. Biologic therapy
 - If the patient is prescribed biologic therapy
 - VI. Others:
 - Asthma education
 - Inhaler use education.

A real-life study on asthma control reported that physicians believed that the main reasons for lack of asthma control included comorbidities, as seen in 36.2% of patients, continued exposure to irritants/triggers in 34.0% of patients, and inadequate adherence to treatment in 27.0% of patients.²⁸

Treatment management plan

Asthma patient management practices among adults have been found to be inadequate in many practices in Europe.²⁹ Along with the information that ISAR will collect on clinical outcomes and demographic characteristics, the best treatment management plan by patient group will be assessed. Moreover, the panel agreed to collect broad treatment options to ensure that all participating countries will be able to contribute without subsection to individual country specifications.

Strengths and weaknesses

The Delphi panel was composed of international severe asthma professionals to ensure that recommendations recognized and reflected all social nuances specific to the participating countries while maintaining applicability in more than 1 health care setting and location. Eighteen unique Delphi panel members from 16 different countries participated in 1 or more Delphi rounds. This allowed broad consensus to be obtained. Using a group approach ensured that more comprehensive expertise was extrapolated than from any individual member alone. The selected panel of experts were chosen not only for their expertise in the research field, but also for their relevant medical practice and experience with developing and/or managing databases or regional/national severe asthma registries. The Delphi method ensured versatility of application and enhanced the sustainability of ISAR in the field due to panel members’ involvement and cooperation in the generation of the registry data specification.

The anonymity of the survey helped to reduce the influence of dominant individuals that may become apparent during face-to-face meetings. However, the anonymity may also have reduced the positive effects of interaction during face-to-face meetings, depriving experts of important exchanges of information that would help to identify and discuss reasons for disagreement.³⁰ The modified Delphi process maximized the benefits of both consensus methods through the initial collection of information via questionnaires followed by structured in-person meetings. ISAR meetings were organized to allow panel and/or steering

committee members to discuss variables and selection criteria and resolve remaining disagreements face to face.

The Delphi process was predominantly carried out online and was therefore efficient and economically viable in terms of investigator time and funding. Furthermore, it facilitated rapid communication between a global panel of experts. However, the response rate was not 100%, with a total of 18 of 27 experts (62%) responding to the 3 Delphi rounds. Although early experiments using Delphi suggested that group error was reduced with increased group size,³¹ more recent studies have found that reliable outcomes can be obtained with a relatively small number of Delphi experts.³² The number of specialized experts in a specific field may be limited. The consistency of expert training may allow small numbers of experts to reliably participate in the generation of valid stable responses. The selection of the panel is therefore extremely important. However, because of the consistency in the number of experts who participated in each round (R1 = 15, R2 = 13, R3 = 14), the possibility of reaching a consensus was conserved.

The Delphi panel was not fully representative of the diversity amongst stakeholders of respiratory health, such as health care payers or patients. The wide range of opinions gathered could be bolstered with an increase in the variety of stakeholders.

The design of the Delphi process, which involved the gathering of opinions from a group of experts, dilutes the opinion of a single expert. Thus, bias is decreased and diversity within the expert panel is maximized, which in turn decreases the possibility of overlooking the obvious facets of the questions. Despite the incomplete response rate and possible changes in experts participating in each round, the final results covered a wide range of areas where consensus was achieved. It is important to remember that the Delphi method is a tool to be used in conjunction with other processes that can be used to answer a wide range of research questions.

It is beyond the scope of this study to investigate the reasons behind the convergent or divergent views of the panel. However, these reasons should be explored next to further validate the methodology of a Delphi exercise.

CONCLUSIONS

Using the Delphi process to gain an international consensus among severe asthma experts across 16 countries, a standardized

framework was developed to describe patients with severe asthma, which may help to define a link between best practices and improved outcomes. These questions cover a comprehensive range of variables from patient demographics, diagnostics, patient- or physician-reported outcomes, and treatment management plans. Collecting a minimum necessary amount of real-life data on a patient with severe asthma will not only enhance the quality of patient care but also ensure the sustainability of ISAR as an international registry given that there are often limited resources available for data collection. This is the first attempt to develop such a registry on a global scale within the setting of severe asthma. The main goal of this effort is to standardize data collection to enable pooling of multiple data sources and assist in clinical decision making for health care professionals around the world. The next step is to enroll patients and collect data that will allow gaps in diagnosis and treatment to be identified, and solutions to be found, which will help bridge these gaps and thus bring us 1 step closer to controlling severe asthma.

Acknowledgments

The International Severe Asthma Registry is conducted by Optimum Patient Care Global Limited, and cofunded by Optimum Patient Care Global and AstraZeneca.

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ONLINE REPOSITORY

TABLE E1. International Severe Asthma Registry Delphi panel members

Delphi panel member	Country
David Price (independent facilitator)	Singapore
Liam G. Heaney	United Kingdom
Andrew Menzies-Gow	United Kingdom
Giorgio Walter Canonica	Italy
Eric Van Ganse	France
Manon Belhassen	France
Roland Buhl	Germany
Anke-Hilse Maitland-van der Zee	The Netherlands
Leif Bjerner	Sweden
Peter Gibson	Australia
Vibeke Backer	Denmark
Chin Kook Rhee	South Korea
Nikos Papadopoulos	Greece
Rohit Katial	USA
Lauri Lehtimäki	Finland
J. Mark FitzGerald	Canada
Guy Brusselle	Belgium
Luis Perez de Llano	Spain
Francisco de Borja Garcia-Cosio Piqueras	Spain
Loo Chian Min	Singapore
Sven Erik Dahlen	Sweden
Mark Hew	Australia
Matthew Peters	Australia
Erin Harvey	Australia
Katia M.C. Verhamme	The Netherlands
Job F.M. van Boven	The Netherlands
Mohsen Sadatsafavi	Canada

TABLE E2. Delphi R1 results summary

R1 variable summary	Number	Criteria	Remarks
Potential core variables			
Total number of variables	115		
Undecided	6	50% to 66.6%	Entered in R2
Without consensus	1	<50%	Removed from core
Less than complete consensus	80	>66.6% and <100%	Entered in R2
Complete consensus	28	100%	Included in core
Suggested variables			
Total number of variables	632		
Highly suggested	54	≥2 suggestions	Entered in R2

TABLE E3. Delphi R2 results summary

R2 variable summary	Number	Criteria	Remarks
Potential core variables			
Total number of variables	86		
Undecided	8	50% to 66.6%	Entered in R3
Without consensus	4	<50%	Removed from core
Consensus	74	>66.6%	Included in core
Suggested variables			
Total number of variables	54		
Highly suggested	9	≥2 suggestions	Consolidated to 4 at inaugural SC meeting and entered in R3

SC, Steering Committee.

TABLE E4. Delphi R3 results summary

R3 variable summary	Number	Criteria	Remarks
Total number of variables	12		
Consensus	4	>66.6%	Included in core
Undecided	5	50% to 66.6%	1 included in core 4 removed from core
Without consensus	3	<50%	Removed from core