Development of the International Severe Asthma Registry (ISAR): a modified Delphi study

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Funding

This study is co-funded by Optimum Patient Care Global and AstraZeneca.

Declarations of Interest

Chris Price, Lakmini Bulathsinhala, Nevaashni Eleangovan, Thao Le, Martina Stagno d'Alcontres, and Victoria Carter are employees of Optimum Patient Care, a co-funder of the International Severe Asthma Registry. Trung Tran is an employee of AstraZeneca, a co-funder of the International Severe Asthma Registry. Gokul Gopalan was formerly an employee of AstraZeneca.

Liam Heaney has taken part in advisory boards and given lectures at meetings supported by GlaxoSmithKline, Respivert, Merck Sharpe & Dohme, Nycomed, Boehringer Ingelheim, Teva, 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.

Andrew Menzies-Gow declares grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Hoffman La Roche; consultancy agreements with AstraZeneca and Vectura; personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hoffman La Roche, Napp Pharmaceuticals, Novartis, Teva and Vectura; non-financial support from AstraZeneca, Boehringer Ingelheim and Napp Pharmaceuticals; and payment for travel expenses to international conferences from AstraZeneca, Boehringer Ingelheim and Napp Pharmaceuticals.

Peter Gibson declares grants from AstraZeneca, GlaxoSmithKline and Novartis; and personal fees from AstraZeneca and GlaxoSmithKline.

Matthew Peters declares personal fees and non-financial support from AstraZeneca and GlaxoSmithKline.

Mark Hew declares grants and other advisory board fees from AstraZeneca, GlaxoSmithKline, Novartis and Seqirus, with all payments to his institutional employer.

Lauri Lehtimäki declares personal fees for consultancy and lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, Novartis, Orion Pharma and Teva; and personal fees for consultancy from ALK.

Eric van Ganse declares grants from ALK ABELLO, Bayer, BMS, GlaxoSmithKline, Merck Sharp and Dohme; and personal fees from ALK ABELLO, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, GlaxoSmithKline, IMS, and Merck Sharp and Dohme.

Luis Perez de Llano declares grants from AstraZeneca, Chiesi and Teva; personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Esteve, GlaxoSmithKline, Mundipharma, Novartis, Sanofi and Teva; non-financial support from Boehringer Ingelheim, Esteve, GlaxoSmithKline, Menarini, Mundipharma, Novartis and Teva.

Anke H. Maitland-van der Zee declares unrestricted grants from GlaxoSmithKline and personal fees for advisory board activities from AstraZeneca.

Nikolaos Papadopoulos declares personal fees for advisory board activities from BIOMAY, Faes Farma, HAL, Novartis and Nutricia Research; consultancy fees from MEDA, Menarini and Novartis; institution grant from Menarini; personal fees for speaker/chairperson from Abbvie, Danone, MEDA, MSD, Novartis and Omega Pharma.

Chin Kook Rhee declares consultancy and lecture fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, MSD, Mundipharma, Novartis, Sandoz, Takeda and Teva-Handok.

Katia Verhamme works for a research group which in the past received unconditional research grants from Yamanouchi, Boehringer Ingelheim, Novartis and GlaxoSmithKline.

Roland Buhl declares personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Novartis, Roche and Teva, as well as grants to Mainz University from Boehringer Ingelheim, GlaxoSmithKline, Novartis and Roche.

Borja G Cosio 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.

David Price declares board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva

Pharmaceuticals; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, 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, 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, Teva Pharmaceuticals; payment for manuscript preparation from Mundipharma, Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma, Novartis; payment for travel/accommodation/meeting expenses from Aerocrine, AstraZeneca, Boehringer Ingelheim, Mundipharma, Napp, Novartis, Teva Pharmaceuticals; funding for patient enrolment or completion of research from Chiesi, Novartis, Teva Pharmaceuticals, Zentiva (Sanofi Generics); 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 Assessment.

Vibeke Backer declares collaboration, consultancy, unrestricted grants and lecture fees from AstraZeneca, TEVA, Sanofi, Boehringer Ingelheim, GlaxoSmithKline, MSD, Mundipharma, Novartis, and Sandoz, furthermore advisory board at AstraZeneca, GSK, ALK-Abello, TEVA, Sanofi, and Novartis.

Celeste Porsbjerg, Erin Harvey, G Walter Canonica, J Mark FitzGerald, Job van Boven, and Manon Belhassen declare no relevant conflicts of interest concerning this paper.

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.

Abstract

Background: The lack of centralised 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 standardised data collection, subsequently enabling data interoperability.

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

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 three 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. Finalisation of the core variable list was facilitated by two face-to-face meetings.

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 non-adherence and information about treatment and management strategies will also be recorded.

Conclusion: This is the first global attempt to generate an international severe asthma registry using a common set of core variables to ensure that data collected across all participating countries are standardised.

Key words: Severe asthma, Disease registry, Delphi process

Abbreviation

A&E	Accident & Emergency
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ADEPT	Anonymised Data Ethics & Protocol Transparency
Anti-IgE	Anti-Immunoglobulin E Treatment
Anti-IL-5	Anti-Interleukin-5 Treatment
ATS	American Thoracic Society
BMI	Body Mass Index
BSA	Body Surface Area
BTS	British Thoracic Society
CRF	Case Report Form
CT	Computerised Tomography
DEXA	Dual Energy X-ray Absorptiometry
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERS	European Respiratory Society
FDA	Food and Drug Administration
FENO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Flow in one second
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
ICS	Inhaled Corticosteroids
IgE	Immunoglobulin E
ISAR	International Severe Asthma Registry
ISC	ISAR Steering Committee
LABA	Long-Acting Beta-Agonists
LAMA	Long-Acting Muscarinic Antagonist
LTRA	Leukotriene Receptor Antagonist
OCS	Oral Corticosteroids
OPC	Optimum Patient Care
OPCRD	Optimum Patient Care Research Database
OPRI	Observational and Pragmatic Research Institute Pte. Ltd.
PC_{20}	Concentration of Methacholine/Histamine needed to produce a 20% decrease in FEV_1
PEF	Peak Expiratory Flow

Abbreviation	
R1	Delphi Round 1
R2	Delphi Round 2
R3	Delphi Round 3
RAST	Radioallergosorbent Test
SABA	Short-Acting Beta-Agonists
SAWD	Severe Asthma Web-based Database
SPT	Skin Prick Test

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156 **Metrics information**:

157 Date: 17th April 2018

158 Abstract word count: 250 words

159 Text word count: 4252 words

160 Number of references: 31 references

161 Number of tables and figures: 3 tables and 2 figures

162 Online supplement: yes, with 4 e-Tables

Introduction

Asthma affects 5–15% of the population worldwide and its prevalence has noticeably increased in recent decades (1). This heterogeneous disease, characterised 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 minimisation of current symptoms and prevention of acute exacerbations using a stepwise approach to medication (2).

Although most asthma patients have mild to moderate disease symptoms that may be well-controlled with standard treatment, a smaller sub-population remains uncontrolled and/or suffers from severe symptoms. The exact prevalence of severe asthma is uncertain but has been estimated at 5–10% of the asthma population (3-5). Such patients remain inadequately managed with the current standard of care (3), which includes high-dose inhaled corticosteroids with additional controllers and represent a significant unmet need.

There is compelling evidence to suggest that better standardised care for severe asthma is needed, including the registration of systematic assessment and improved and aligned registries of patients whose symptoms fulfil 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 which 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 post-approval 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 organisations. These disparities can lead to country-specific registries collecting different data fields of various quality. 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 sub-populations 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 Kingdom (UK) (9) and Australia (11, 13), our aim was to gain expert consensus on a standardised 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 utilised a modified, 3-round Delphi method process (14) 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 usage 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 (Supplementary Table 1), and were selected according to two or more of the following criteria:

1. Evidence of relevant asthma research published in high-ranking peer reviewed journals (e.g. 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 five Delphi panel members not on the ISC were: one pharmaco-epidemiologist, one health-economist, two severe asthma clinical researchers, and one severe asthma database manager.

Modified Delphi process

A modified Delphi process was used to reach consensus (15). The process consisted of three 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 two-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 (British Thoracic Society (BTS) Difficult Asthma Network) (9) 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 two sets of variables: there were 115 variables in the "potential core" list (variables common to both registries; please see Table 1 for a sample) and 632 variables in the "suggest" list (variables unique to either registry; please see Table 2 for a sample).

The workbook was developed using Microsoft Excel 2016 MSO (V16.0) and consisted of a two-tab spreadsheet with response-controlled questionnaires. On tab one, displaying the potential core list (Table 1), 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 variable list. Panel members were also encouraged to nominate variables from the suggest variable list (Table 2) on tab two 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 anonymised 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, Texas, USA). 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 two “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 ISAR Steering Committee meeting in March 2017.

Delphi R2

As in R1, the expert panel was requested to engage in a similar voting process for the 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 anonymised 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 registry 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. Additionally, suggest variables with at least two 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, following finalisation of *suggest* variables during R3 discussions by the Delphi panel. *Suggest* variables from R2 which had attained more than 50% consensus and potential core

284 variables from R2 on which a consensus was not reached (>50% and <66.6% consensus) were circulated
285 for another round (R3). In addition, due to high relatability, nine of the suggest variables from R2 were
286 consolidated into four variables/questions after discussion at the inaugural Steering Committee meeting.
287 These were: current occupation, age at start of asthma symptoms, environmental allergen test
288 conducted, and current clinical management plan. These variables were added to the R3 workbook to
289 ensure full vetting and review by the panel.

290 The ISAR core variables were finalised during the second ISAR Research Prioritisation meeting in May
291 2017. R3 results and all outstanding concerns raised by panel members, such as data field options for
292 variables including ethnicity and occupation, were discussed and resolved at the second Steering
293 Committee face-to-face meeting. The participants were requested to re-evaluate the remaining five
294 undecided variables to arrive at a consensus on which variables would be submitted for another Delphi
295 round and hence, which would be retained or removed from the final ISAR core variable list. The
296 discussion was mediated by the Delphi neutral facilitator, who closed the gap of consensus by reminding
297 the Steering Committee and/or Delphi members of the aim of the ISAR registry and the international
298 study population under consideration. The final core variable list was shared with the Delphi panel in a
299 Case Report Form (CRF). All chosen core variables were represented in the final CRF questionnaire
300 format.

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

Data Sharing

For the three types of variable lists shown below, the corresponding variable name and the related meta-data, 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 Non-matching variables from the BTS and SAWD registries)
3. Sheet 3: Variables disqualified
   (List of variables removed from the total number of matching and non-matching variables)

This data has been deposited into a secure electronic repository via Mendeley Data (http://dx.doi.org/10.17632/xdrdy37tbm.3).

Results

Delphi R1

Fifteen of the 27 members of the panel participated in Delphi R1 (55.6%); 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, six were undecided (50–66.6%) and one variable did not achieve consensus (<50%) (Supplementary Table 2). 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.

Additionally, 54 suggest variables had attained at least two or more votes by the Delphi panel and moved on to the second round of the Delphi process (R2) (Supplementary Table 2). 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) asthma control questionnaire and patient status as a research subject. The asthma medication question regarding anti-leukotriene 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, eight were undecided and four did not achieve consensus. In addition, nine of 54 variables in the suggest variable list attained more than 66.6% agreement for inclusion into the ISAR core variable list (Supplementary Table 3).

Of the eight undecided variables, comorbidities (Ischaemic Heart Disease and Heart Failure), asthma medication (Inhaled corticosteroid [ICS], Long-acting beta-agonist [LABA], long-acting muscarinic antagonist [LAMA]) 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 nebuliser, SABA (short acting beta-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 Asthma Control questionnaire was chosen as the patient-reported measure of asthma control, and therefore included in the core variable list. Due to highly related variables, the nine newly suggest variables were consolidated into four variables after detailed discussion and review among the Delphi panel. Altogether, eight undecided potential core variables and the four 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 (Supplementary Table 4). Of the remaining eight variables, five were undecided, and three did not achieve consensus. Upon review by the Delphi neutral facilitator, and a face-to-face discussion with the Steering Committee in May 2017, one undecided variable was included into the core variable list. All three non-consensus variables and remaining four undecided variables were removed from the core list. R3 resulted in five variables added to the core variable list. With all "potential core" variables achieving a status of consensus or non-consensus, the Delphi exercise ended at R3.

To further streamline the process, undecided variables and non-consensus 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 ISAR Steering Committee 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 two 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 were 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 two or more courses of oral corticosteroids.

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

Final ISAR core variable list

The core variables that achieved consensus via the closely guided three rounds of Delphi were included in the final core variable list (Table 3). 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 (auto-populated). 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 International Severe Asthma Registry. 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 severe asthma patients in a real-world setting. These criteria served the primary purpose of the registry to prospectively survey severe asthma patients. In addition, the inclusion criteria allowed the core data to be used for broader purposes (e.g. 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 in order 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 healthcare 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 categorised (16). The panel-approved variables were chosen to ensure 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 (17-19). The GINA questionnaire 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 to other available questionnaires (20).

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 (FENO) have been shown to be useful for the management of asthma (21, 22), and may help identify specific subtypes of severe asthma likely to benefit from treatment with novel biological agents.

Adherence and comorbidities

Non-adherence to therapy is approximately 50% in adults with severe asthma (23-25). Physicians need to ensure that patients are satisfied with their medication to increase adherence and optimise disease control (26). The potential for ISAR to investigate non-adherence across different geographical regions, with likely different healthcare systems, availability of medications and access to specialists and asthma education, was noted.

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 (27).

Treatment management plan

Asthma patient management practices among adults have been found to be inadequate in many practices in Europe (28). Along with the information that ISAR will collect on clinical outcomes and

444 demographic characteristics, the best treatment management plan by patient group will be assessed.
445 Moreover, the panel agreed to collect broad treatment options to ensure that all participating countries
446 will be able to contribute without subjection to individual country specifications.

447 ## Strengths and weaknesses

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

459 The anonymity of the survey helped to reduce the influence of dominant individuals which may become
460 apparent during face-to-face meetings. However, the anonymity may also have reduced the positive
461 effects of interaction during face-to-face meetings, depriving experts of important exchanges of
462 information which would help to identify and discuss reasons for disagreement (29). The modified
463 Delphi process maximised the benefits of both consensus methods through the initial collection of
464 information via questionnaires followed by structured in-person meetings. ISAR meetings were
465 organised to allow panel and/or steering committee members to discuss variables and selection criteria
466 and resolve remaining disagreements face to face.

467 The Delphi process was predominantly carried out online and was therefore efficient and economically
468 viable in terms of investigator time and funding. Furthermore, it facilitated rapid communication
469 between a global panel of experts. However, the response rate was not 100%, with a total of 18 out of
470 27 experts (62%) responding to the three Delphi rounds. Although early experiments using Delphi

suggested that group error was reduced with increased group size (30), more recent studies have found that reliable outcomes can be obtained with a relatively small number of Delphi experts (31). The number of specialised 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, due to 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 healthcare 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 maximised, 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 which 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.

Conclusion

Using the Delphi process to gain an international consensus among severe asthma experts across sixteen countries, a standardised 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 severe asthma patient 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 standardise data collection to enable pooling of multiple data sources and assist in clinical decision-making for healthcare professionals around the world. The next step is to enrol 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 one step closer to controlling severe asthma.

Acknowledgements

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

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591 **Table 1: Sample of the "Potential Core" variable list from the International Severe Asthma Registry Delphi**
592 **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				

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594

595 **Table 2: Sample of the "Suggest" variable list from the International Severe Asthma Registry Delphi**
596 **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		10^9/L		
	Macrophages	Decimal		%		
	Lymphocytes	Decimal		%		
	Samples stored locally for biobanking	Radio button	No/Yes			

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598 **Table 3: 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: a. Having severe asthma symptoms including poor symptom control, airflow limitation, and serious exacerbations b. Frequent severe asthma exacerbations requiring systemic corticosteroids. Patient fulfils 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 months Number of episodes of invasive ventilation ever Number of A&E attendances for asthma in the past 12 months Number of hospital admissions for asthma in the past 12 months
Comorbidity	Eczema Allergic Rhinitis Chronic Rhinosinusitis Nasal Polyps Atopic Disease (Atopic Dermatitis and allergic rhinitis).

599

600 **Table 3: Cont.**

Category	Variable Field Name
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	Pre-bronchodilator FEV1 Post-bronchodilator FEV1 Pre-bronchodilator FVC Post-bronchodilator FVC Predicted FEV1 Pre-bronchodilator FEV1 (% predicted) Post-bronchodilator FEV1 (% predicted) Predicted FVC Pre-bronchodilator FVC (% predicted) Post-bronchodilator FVC (% predicted) FEV1/FVC ratio pre-bronchodilator (%) FEV1/FVC ratio post-bronchodilator (%) PC20 methacholine/histamine test Date of PC20 test PC20 test result Fractional Exhaled Nitric Oxide (FENO) test Date of FENO test FENO test result

601

602 **Table 3: Cont.**

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 weeks, 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 Theophyllines 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

603

604 **Table 3: Cont.**

Category	Variable Field Name
Adherence	Evidence of poor adherence[1]
Management Plan	Other factors contributing to severe asthma symptoms[2] Current Clinical Management Plan[3]

[1] "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):

(a) **Subjective measure (e.g. Clinical Impression, self-ending)**: Opinion of a medical personnel for poor adherence to asthma medication therapy or patient self-report
- For example[32].
  i. Impression of "Non-persistence": Patient stops taking medication.
  ii. Impression of "Non-implementation": Patient does not take medication as prescribed.

(b) **Objective measure (e.g. 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:
  i. **Medication Possession Ratio (MPR)**= (Sum of days' supply for all fills/Number of days) X 100% <80% threshold

[2] "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)
  - Strong smells (Perfumes)
  - Prior Respiratory Infections

[3] "Current Clinical Management Plan":
This variable aims to record the asthma action plan for a patient to review efficacy over time.
- For example:
  - Entry into Clinical Trial
    - If the patient is deemed suitable to benefit from a clinical trial drug
  - Discharge to local asthma service
    - If the patient has shown alleviated asthma symptoms
  - Optimisation of current asthma therapy
    - If the patient's current asthma therapy is titrated for better asthma management
  - Bronchial Thermoplasty
    - If the patient is eligible to have a bronchial thermoplasty surgery to manage their asthma
  - Biologic Therapy
    - If the patient is prescribed biologic therapy
  - Others:
    - Asthma education
    - Inhaler use education

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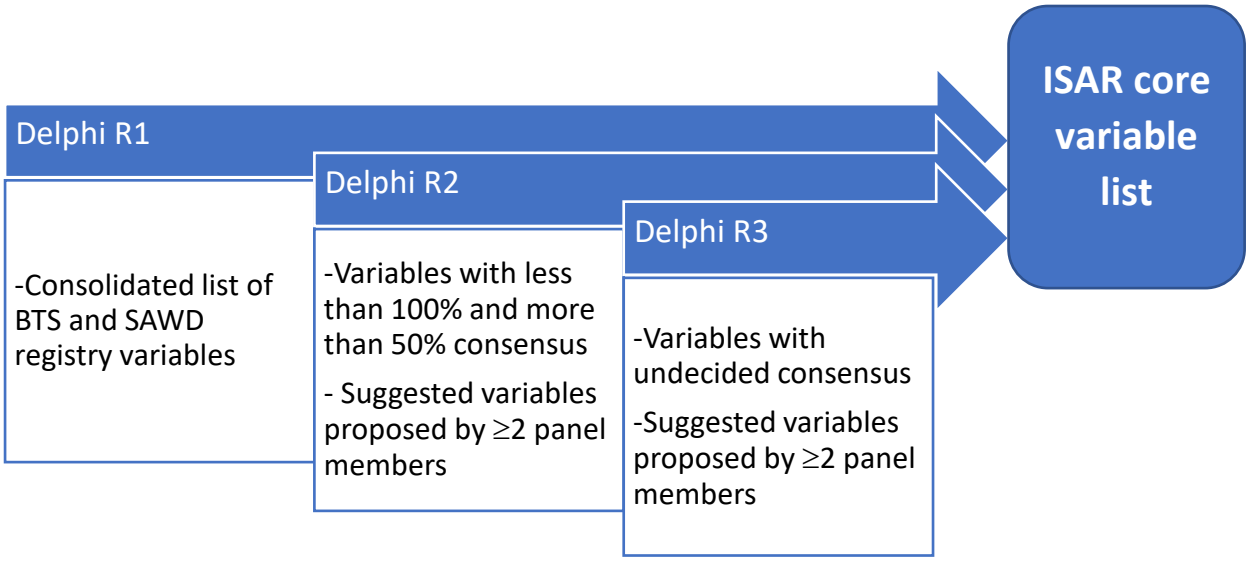
606 **Figure Legend**

607 **Figure 1: General flow of the International Severe Asthma Registry (ISAR) Delphi process showing topics**
608 **discussed in each round**

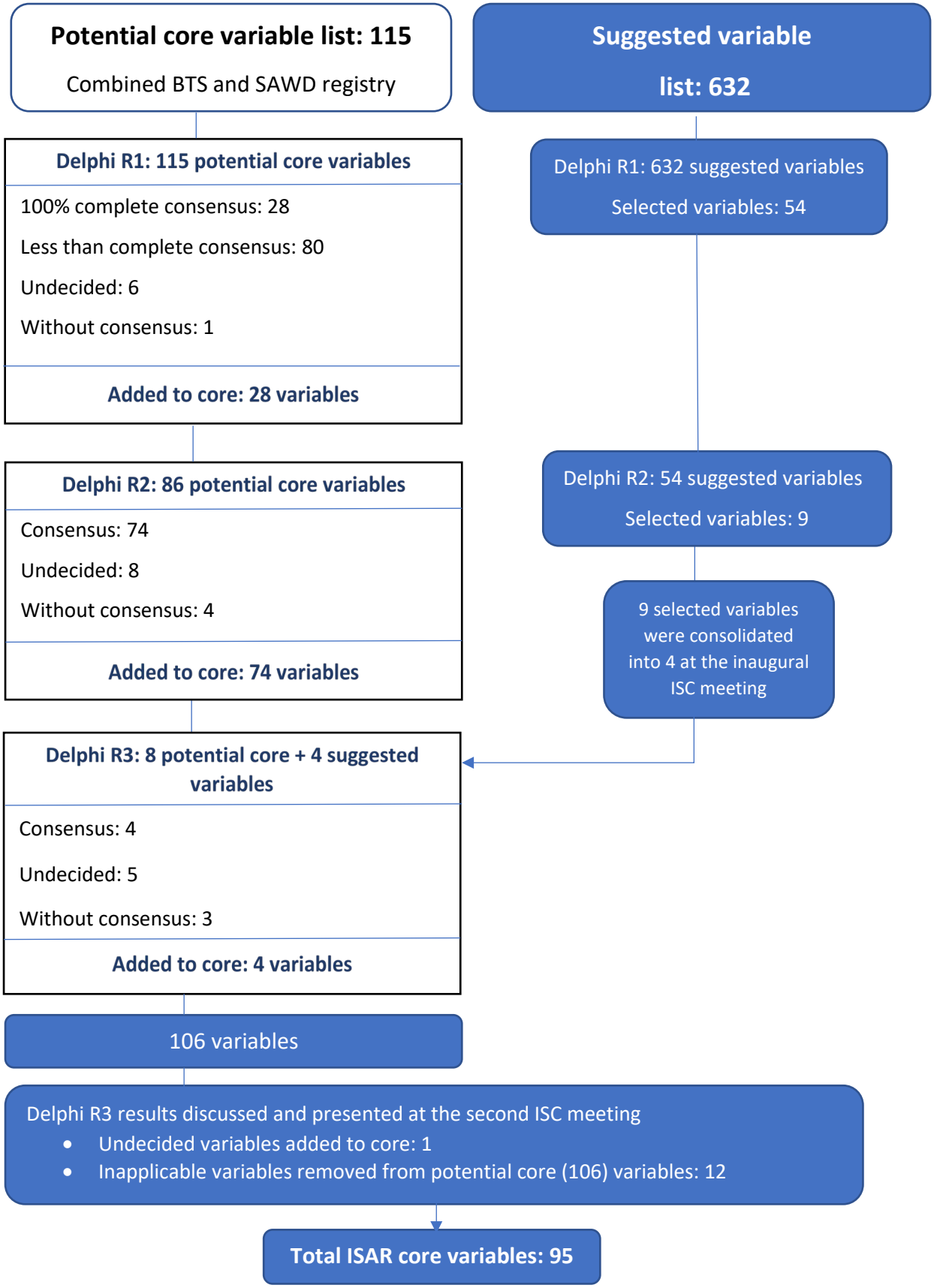
609 **Figure 2: Summary of Delphi results for the International Severe Asthma Registry (ISAR)**

610

611



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



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

Supplementary Material

Supplementary Table 1: International Severe Asthma Registry Delphi panel members

Delphi Panel Member	**Country**
David Price (independent facilitator)	Singapore
Liam 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 Bjermer	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 FM van Boven	The Netherlands
Mohsen Sadatsafavi	Canada

Supplementary Table 2: 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

Supplementary Table 3: 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 the inaugural SC meeting and entered in R3

Supplementary Table 4: 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