ISAR Registry Protocol

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International Severe Asthma Registry: Protocol

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PROJECT DELIVERY COLLABORATORS

Optimum Patient Care (OPC) Global in collaboration with its not-for-profit affiliate OPC Ltd, specialises in delivering medical research and services to improve the diagnosis, treatment and care of chronic diseases within Primary Care. OPC has a proven track record in delivering primary care research, clinical support services, bespoke data sets for academic research as IG-compliant data extractions and delivering global registry projects. One such example is "Inhaler technique assessment initiative Helping Asthma in Real-life Patients" (iHARP) project. In the UK, OPC has over 10 years' experience conducting real life research and currently working with 600 Primary care sites. OPC has established one of the largest respiratory care database, Optimum Patient Care Research Database (OPCRD) in the world. The OPCRD is a unique database that has over 3.5 million electronic health records providing information on patient reported data from 50,000 patients with asthma. OPC has also delivered and is the guardian of the iHARP database with patient review data from nearly 5000 patients across eight (8) different countries: UK, Netherlands, Norway, Spain, Italy, Sweden, Australia and France. These databases have generated key data relating to asthma patients and have been utilised in over 48 research projects and publications

The Respiratory Effectiveness Group (REG) is a not-for-profit investigator led academic initiative comprising of over 420 respiratory/allergy experts globally collaborating on delivering independent, academic real-life and comparative effectiveness research in respiratory medicine. The REG initiative focuses on establishing best practice methodologies and standards, with the objective of raising the quality and profile of real-life research for all stakeholders including patients, clinicians, industry and guideline/regulatory bodies. Within REG, there are focused Scientific Research Working Groups and quality standards committees whose aims are to:

- Provide ethical and scientific review of real-life research study protocols
- Communicate best practice, establishing quality standards through its research and activities, lead in providing examples of excellence in real-life research
- Establish quality standards in the field of real-life research and improve understanding of the optimum role of real-life data to inform meaningful clinical practice guidelines, drug licensing and post-marketing surveillance processes and improve patient care
- Focus on specific disease topics to generate initiatives and research in that area. This includes the Severe Asthma / Biomarkers Working Group which has proposed this initiative.

OPC supports REG in the following:

- Academic support by provision of free access to the OPCRD
- Bespoke data sets for academic real-life research via the OPCRD
- Statistical and academic leadership.

OPC works collaboratively with REG experts to enable the delivery of independent real-life academic research. One example of a current ongoing collaboration between OPC and REG is the COPD Control project being delivered across seven countries namely Ireland, Malta, Poland, Singapore, Spain, South Korea and the UK.

ISAR CORE STEERING COMMITTEE

REG's inter-disciplinary Scientific Research Working Groups represent a network of researchers working in collaboration to identify unmet research needs through non-randomised controlled trial studies and deliver high-quality academic research in the field. The ISAR core panel members' collective expertise, scientific knowledge and experience in database and research, form an essential element to the ISAR initiative.

Listed below, are the names of the core expert panel members who will be the drivers in the delivery of the registry globally.

- **David Price**, Singapore, MD, Primary Care Respiratory Society UK, President of Observational and Pragmatic Research Institute (OPRI), Professor of Primary Care Respiratory Medicine, University of Aberdeen. Past president of the Respiratory Effectiveness Group
- **Liam Heaney**, United Kingdom, MD, Clinical Professor at School of Medicine, Dentistry and Biomedical Sciences, Queen's University, Belfast, Ireland, Co-founder of BTS UK Severe Asthma Network and National Registry on Difficult Asthma
- **Giorgio Walter Canonica**, Italy, MD, PhD, Secretary General, World Allergy Organization, Professor, Allergy and Respiratory Diseases Chairman, Allergy and Respiratory Diseases Clinic Director, Specialty School of Pulmonary Diseases, Genoa University, Genoa, Italy. REG Executive Officer
- **Enrico Heffler:** Italy, MD, Personalized Medicine Asthma & Allergy Clinic, Humanitas University & Research Hospital, Milan, Italy
- **Elisabeth Bel**, Netherlands, MD, PhD, Professor of Respiratory Medicine and Pulmonary Diseases at the Academic Medical Centre, University of Amsterdam
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- **Leif Bjermer**, Sweden, MD, Professor, Senior Physician, Lund University, Sweden, Professor, MD, Head of the Department of Respiratory Medicine and Allergology, University Hospital, Lund
- **Vibeke Backer**, Denmark, MD, Clinical Professor of Copenhagen University Hospital, Denmark
- **Andrew Menzies-Gow**, United Kingdom, MD, Consultant in Respiratory Medicine, Director – lung division, Royal Brompton Hospital, London, UK. Co- founder of BTS UK Severe Asthma Network and National Registry on Difficult Asthma
- **Nikos Papadopoulos**, Greece, MD, PhD, Professor of Allergy and Paediatric Allergy and Past President of the European Academy of Allergy and Clinical Immunology (EAACI), REG Executive Officer

- **Eileen Wang**, USA, MD, MPH, Assistant Professor, Division of Allergy & Clinical Immunology, Department of Medicine, National Jewish Health
- **Mark Fitzgerald**, Canada, MD, Head of University of British Columbia (UBC) Division of Respiratory Medicine, Canada. Co-Director of Institute of Heart and Lung Health.
- **Mohsen Sadatsafavi**, Canada, MD, PhD, Assistant Professor, Health Outcomes, Associate, Division of Respiratory Medicine, UBC Scientist, Centre for Clinical Epidemiology and Evaluation, University of British Columbia, Canada
- **George Christoff**, Bulgaria, MD, PhD, Professor and Department Head at Medical University Sofia, REG Member
- **Peter Gibson**, Australia, MD, Respiratory physician, John Hunter Hospital, New South Wales, Australia, Clinical researcher and Co-Director of the HMRI Viruses, Infections/Immunity, Viruses and Asthma research program, Co-Director University of Newcastle Priority Research Centre (PRC) for Asthma and Respiratory Diseases. President of the Thoracic Society of Australia and New Zealand Australia
- **Mark Hew**, Australia, MD, PhD, Associate Professor Royal Melbourne Hospital, Clinician Researcher, Alfred and Royal Melbourne Hospitals, Head of the Allergy, Asthma and Clinical Immunology Service, Alfred Hospital
- **Roland Buhl**, Germany, MD, PhD, Professor of Medicine and Head of the Pulmonary Department at Mainz University Hospital, Germany. Editor of Respiratory Medicine.
- **Chin Kook Rhee**, South Korea, MD, PhD, Division of Allergy, Pulmonary and Critical Care Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, South Korea
- **Luis Perez-de-Llano**, Spain, MD, Head of the Pulmonology Unit, Lucus Augusti Hospital of Lugo, Director of the Training and Teaching Committee of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR)
- **Francisco de Borja Garcia-Cosio Piqueras**, Spain, MD, PhD, Respiratory Medicine, Department of Pulmonology, Hospital Universitari Son Espasas, Spain
- **Lauri Lehtimaki**, Finland, MD, Associate professor of Respiratory Medicine, University of Tampere
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- **Sverre Lehmann**, Norway, MD, PhD, Associate Professor, University of Bergen, Haukeland University Hospital, Bergen, Department of Thoracic Medicine
- **Alan Altraja**, Estonia, MD, Department of Pulmonology, Head of Clinic, Professor of Pulmonology, University of Tartu, Estonia
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- **Unnur Björnsdóttir**, Iceland, MD, Faculty of Medicine, Clinical Immunology, Allergology, Landspitali University Hospital, Reykjavík
- **Richard Martin**, USA, MD, Professor, Chairman, Department of Medicine, National Jewish Health, Professor, National Jewish Medical and Research Center and the University of Colorado Health Sciences Center, Denver, Chairman, Edelstein Family Chair in Pulmonary Medicine.
- **Richard Costello**, Ireland, MD, Associate Professor, Beaumont Hospital, Department of Medicine, Clinical Research Centre-Royal College of Surgeons in Ireland
- **Matthew Peters**, MD, PhD, Respiratory Physician, Head of Respiratory Medicine, Concord Hospital. Professor, Woolcock Institute of Medical Research, Macquarie University and Sydney University.
- **Arnaud Bourdin**, France, MD**,** PhD, Professor and Respiratory Physician, Department of Pneumology, Hospital Arnaud de Villeneuve, CHRU, Montpellier, France
- **Camille Taillé**, France, MD, PhD, Respiratory Physician, Department of Pulmonology and Allergology, Hôpital Bichat Claude Bernard, Paris, France
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- **Rupert Jones,** UK, MD, Respiratory Research Unit, Peninsula Medical School, University of Plymouth, Devon
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- **Trung Tran**, USA, MD, Director, Epidemiology, AstraZeneca, USA

PROTOCOL SYNOPSIS

The international Severe Asthma Registry (ISAR) is a global collaborative initiative to gather anonymous longitudinal real-life data for patients with severe asthma from over 14 countries. The ISAR initiative is conducted by Optimum Patient Care Global Limited (OPC), with academic and regulatory oversight from the ISAR Core Steering Committee (ISC), academic support from the Respiratory Effectiveness Group (REG), ethical governance from the Anonymised Data Ethics & Protocol Committee (ADEPT), with joint funding support from OPC and AstraZeneca.

ISAR will offer a rich source of real-life data for scientific research to understand and improve symptoms, treatments and patient outcomes for severe asthma. The database will also provide an international platform for research collaboration in respiratory medicine.

Participating countries will agree to provide access to and share anonymous patient-level data for ISAR as part of the initiative. Participating countries will contribute high quality and standardised anonymous patient-level data to form research datasets for research studies approved and prioritised by the ISC. Based on the ethical, legal and regulatory permissions for each participating country, anonymous data will be collected into a central repository database (described here as the ISAR Database) for relevant dataset creation and required analysis.

Countries with an existing registry: The ISAR initiative will provide support for aligning variables collected with ISAR core and collecting data for each participating country. Countries with existing and well-established registries will be supported with extracting the required data from their home registries for ISAR.

Countries with no existing registry: The ISAR initiative will provide support for countries with no existing registry to set-up a registry to facilitate data to be collected and contributed to ISAR, among other benefits for the individual country. This support will include support for the use of suitable electronic data entry or capture systems/platforms.

1.0 BACKGROUND & RATIONALE

1.1 Background

Severe Asthma

Asthma is a heterogeneous disease characterised by chronic airway inflammation. It affects 5-15% of people worldwide and shows increasing prevalence over the last decades (1). Treatments aiming to achieve optimal disease control and prevent acute exacerbations using a stepwise approach to medication are well established in national and international guidelines (2). However, due to the lack of an accurate definition of severe asthma, the exact prevalence of the disease is unknown. A UK based study found that the percentage of people with severe uncontrolled eosinophilic asthma was 1% of patients with active asthma (unpublished OPRI and AZ collaboration). A study by Hekking et al. in the Netherlands found that the prevalence of severe refractory asthma, defined as patients with difficult to control asthma, adherent to high dose ICS with good inhaler technique, was <1% of the Dutch adult asthmatic population (3). This suggests that the prevalence of severe asthma, as defined by international consensus, is underestimated in the literature to date. The data presented in these studies define severe asthma as a rare disease (3).

Patients with severe asthma suffer significant impairment in their daily life and incur a major economic health burden. A recent Korean study in 314 patients with severe asthma found that both direct and indirect costs were significantly increased for patients with severe persistent asthma compared to those with mild and moderate disease (5). Despite the availability and use of effective preventive therapy, costs associated with asthma are increasing and affecting both the individual and the healthcare provider. Regardless of the increased understanding of the nature of the disease, the factors that contribute to the destabilisation are as yet unclear and much remains conjectural. Part of the difficulty lies in the definition of asthma severity, evaluated as an arbitrary combination of signs and symptoms present and their intensity.

The Severe Asthma Research Program (SARP) identified different subgroups of severe asthma based on the varied clinical manifestations, pathophysiological mechanisms and biomarkers (4). In this study, 438 subjects with asthma were closely examined. The authors found that patients with severe asthma tended to be older with longer disease duration, daily symptoms, intense urgent healthcare utilisation, sinusitis, and pneumonia. Although the lung function was lower in these patients, lung function abnormalities were reversible upon bronchodilator treatment in most patients (4). Gaining a better understanding of the mechanisms of this disease will ultimately improve therapies.

Biomarkers and phenotypes in the management of severe asthma and predicting treatment response

Patients with mild-to-moderate asthma can be controlled with escalating doses of inhaled corticosteroids (ICS) in conjunction with long-acting β-agonists (LABA) or leukotriene antagonists. In patients with more severe asthma and frequent exacerbations, this therapy may not

be sufficient to control their symptoms and prevent exacerbations. Despite the increasing range of medications and improvements in inhaler design and patient management, asthma related deaths continue to increase, with a reported 17% increase between 2014 and 2015 in the UK alone (6). Novel therapies may help to fill this void. However, new therapies are often expensive, and there is a need to identify patients who are likely to benefit from these treatments.

An emerging tool in disease monitoring and selection of optimal therapy is the assessment of biomarkers. Biomarkers, are traceable substances that can be used to examine organ function or other aspects of health (7), providing information about disease severity and predicted outcomes as well as serving to select the most effective treatment for specific patients.

For example, patients with asthma and significant eosinophilia have been found to be at higher risk of more severe disease (8). Eosinophils can affect airway biology as a source of epithelial damage and airway remodelling in asthma, thus contributing to disease severity. Studies have shown that peripheral blood eosinophilia can be used as a biomarker to predict the effectiveness of anti-IL-5 therapy in the prevention of exacerbations (9, 10, and 11). Recent data suggests that other variables as well as eosinophils can be used to predict frequent asthma exacerbations. These include local eosinophilia such as nasal polyps and comorbidities including diabetes mellitus (12).

Like eosinophil counts, an increase in the fraction of exhaled nitric oxide (FeNO) has been shown to predict asthma exacerbations (13). Raised FeNO is considered a clinical biomarker of inflammation. However, FeNO values have many confounding factors including tobacco smoking, obesity, and corticosteroid use (7). A clearer understanding of the correct conditions in which FeNO plays the role of biomarker in asthma needs to be established, as the ease of use promises expanded use in patients with severe asthma. In particular, combining FeNO and blood eosinophil data may help in predicting who will best benefit from a particular biologic therapy. Furthermore, a significant proportion of patients with asthma have been found to also have allergic sensitisations. The presence of allergen-specific IgE along with allergen exposure are known risk factors for disease expression and severity and along with FeNO and blood eosinophil counts predict treatment response to anti-IgE therapy (7).

Identification of biomarkers will increase understanding of the severe asthma phenotype. This advance in disease characterisation can lead to improved care of severe asthma patients.

National versus International Registries

The Agency for Healthcare Research and Quality (AHRQ) defines patient registries as “an organised system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes” (16). Registries are well-established methods for tracking and reporting clinical outcome, safety, effectiveness and epidemiological endpoints for patients and treatments. They are a valuable resource of the proactive monitoring of the benefit and risk of a treatment over time through collecting natural history data and in developing therapeutics and/or diagnostics. They can be used to: inform understanding of disease progression and patient subgroups; facilitate patient recruitment into clinical trials; and allow the generation of real world evidence on health outcome, safety and effectiveness of new therapeutics.

The current national registry landscape is viewed as a collection of divergent registries. The design, development, and maintenance of patient registries revolve around specific platforms. This leads to the creation of segregated silos resulting in expensive and inflexible systems and little or no collaboration between the different collections. Registries are often built for a single purpose, predominantly making them drug specific, with their own data stores and for limited user profiles resulting in patient numbers that are too low to give any significant power for research. Moreover, different legislation and governance rules and obligations are spread across different countries and organisation types. These limitations lead to the implementation of only a subset of registry functions resulting in the production of only a fraction of the data and often not applying interoperability approaches.

1.2 Rationale

The generation of a global severe asthma registry aims to overcome the current problems encountered when using individual registries. The standardisation of the data collection will aid in establishing interoperability of health data sources globally, as well as the establishment of a clear process for researchers to access the registry to allow data collection and manage their patients with severe asthma. Biomarker data, such as FeNO, eosinophils, and IgE will be an important feature of the severe asthma registry, helping to identify patients that are likely to respond to existing and emerging biologics.

A prime example of what can be achieved with a clear and common purpose and international collaboration is the Translational Research in Europe – Assessment & Treatment of Neuromuscular Diseases (TREAT-NMD), which is a network for the neuromuscular field established to ensure the most promising treatments became available to patients in the shortest time possible. Launched in 2007 under EU funding the network was composed of 350 researchers and clinicians in 22 European organisations which then expanded to include many collaborators from across the world. The success of this network was so great that after the end of EU funding the program was able to continue thanks to funding from patient organisations, academic institutions, and national funding to support patient registries and educational meetings in many countries. The data collected from this network has been published in many high impact factor journals.

Other successful examples include international registries in neuromuscular dystrophy (TREAT-NMD), and multiple sclerosis (EUReMS). The European Register for Multiple Sclerosis (EUReMS) was run between 2011 and 2014 and consisted of two phases. This initiative proved that cross border data collection for MS is possible. The data collected in this registry fuelled four studies that were relevant to both academics and patients living with MS.

The development of an International Severe Asthma Registry (ISAR) of 10,000 patients across 14 countries has the potential to become an important platform for the study and better understanding of this heterogeneous disease as well as support the appropriate use and monitoring of impact of novel asthma therapies.

2.0 OBJECTIVES

The purpose of the registry is to provide a mechanism to store data to enable greater power to answer key research questions in severe asthma across the collaborating countries.

2.1 Primary Objective(s)

The key objectives of establishing the International Severe Asthma Registry (ISAR) initiative are to:

- Describe and characterise the severe asthma patient population natural history overall where appropriate and by different subgroups (e.g. by age, sex, disease severity, exacerbation frequency, different comorbidities, physician type, and also by country to understand regional differences in patient characteristics)

- Facilitate the phenotyping and endotyping of patients with severe asthma and to describe these groups by burden of illness, disease management patterns and clinical evolution in these patient populations in an international setting.

2.2 Secondary Objective(s)

For the overall sample and by subgroups as appropriate, the secondary objectives are to:

- Evaluate the real-life effectiveness and safety of treatments for severe asthma overall and in specific patient groups/phenotypes

- Support the development of effective and efficient diagnostic routines and therapeutic principles

- Improve patient outcomes through structured asthma reviews (short-term) and increased understanding of severe asthma (long-term)

- Minimise side effects of steroid exposure through use of appropriate treatments.

- Assess the level of classification differences as defined by comparing physician-diagnosed severe asthma at baseline against established guidelines' diagnostic criteria

- Describe disease management patterns such as treatment changes over time (e.g. step up, step down, and switches), as well as the reasons for changes and the effect of these changes on clinical progression

- Describe factors associated with treatment choice at baseline and describe disease progression

- Describe risk factors (characteristics at baseline: e.g. age, sex, smoking, BMI, occupation, family history, presence of comorbidities, socioeconomic status, quality of care, lung function, exacerbations associated with disease progression, patient-reported outcomes, and health care resource use.

- Assess the occurrence of exacerbations and other conditions, including Upper Respiratory Tract Infections (URTIs), including seasonal variations

- Assess biomarker data and estimate their predictive value for disease diagnosis, pheno/endotype characterisation, response to treatment, and progression

- To identify patients who may be eligible for participation in future research studies.

3.0 METHODOLOGY

3.1 Registry Design

This registry is a multi-country, multicentre, observational initiative which will retrospectively and prospectively collect data regarding severe asthma patients. The key feature of the International Severe Asthma Registry will be a standardised annualised recording of:

- A key set of severe asthma related data points
- Selected enhanced data points for optional additional data collection
- Standardised coding for data point variables and
- Standardised response options.

Due to its innovative approach with comprehensive data collection, the registry will have a core component where the key variables will be collected creating a large registry platform in which more specific studies addressing particular objectives will be embedded. The details of the sub-studies will be finalised at a later stage. The substudies will be conducted in subsamples of patients from the registry and the countries may choose whether or not to participate in new substudies without jeopardizing their status as ISAR participants. Significant changes in the protocol and new substudies will be reviewed by those entities prior to initiation.

All patients enrolled in the ISAR platform will be followed-up annually during routine clinical visits for a total duration of up to four years.

3.2 Draft Country Initiation

Country participation and recruitment to the ISAR is based on core funding which include countries from Oceania (e.g. Australia), North America (e.g. U.S., Canada), Europe (e.g. France, Germany, Italy, Spain, UK, Nordics) and Asia (e.g. South Korea, Singapore, Japan).

		Core Steering Committee	Existing Registries
Year 1	UK	Liam Heaney	BTS
	Spain	Luis Perez-de-Llano	Setting up: Spain
	Australia	Peter Gibson	SAWD
	Germany	Roland Buhl	GAN
Year 2	Canada	Mark Fitzgerald	
	Italy	Giorgio Walter Canonica	SANI
	France	Eric Van Ganse,	Setting up: France
Year 3	Finland	Lauri Lehtimaki	Setting up: Nordics
	Denmark	Vibeke Backer	Setting up: Nordics
	Netherlands	Anke-Hilse Maitland-van der Zee	
Year 4	Belgium	Guy Bruselle	BSAR
	Japan	Yuji Tohda	
Year 5	USA	Eileen Wang	
	South Korea	Chin Kook Rhee	
Extra – Non-confirmed	Singapore	David Price	
	Norway	Celeste Michala Porsbjerg	Setting up: Nordics
	Sweden	Leif Bjermer	Setting up: Nordics

3.3 Data Collection

Data will be collected by a combination of existing registries and new registries where primary data collection (via eCRFs) will contribute to the development of a web-based platform to host the ISAR. A separate Standard Operating Procedure (SOP) will guide the data collector on how to complete the CRF/eCRF. Another guide will be given to new registry countries on how to use the ISAR EDC systems: REDCap and CISIV.

Two types of data collection approaches are envisioned for the ISAR registry and this may vary from country to country and within a given country.

They are the following:

- **Existing Registries:** This approach utilises a local specific registry that already provides comprehensive data for patients within a catchment area with possible enrichment via prospective data collection. The data collection in these instances will remain with existing systems for example:

- *UK: Dendrite Clinical Systems*
- *Australia: REDCap*

If a local existing registry is used, this will comply with the minimum standards for data collection established by the ISAR Steering Group and agreed by each participating country to enable the combining of datasets across all countries. Data within the registry will be "hashed" so that it can only link back to a particular patient at the patient's local registry site.

- **New Registries:** When registries are not available (at the site or country level), only primary data collection will be implemented. A comprehensive eCRF will be the sole source for medical history, clinical physicians' assessments, and PROs.

    - *REDCap*
    - *CISIV*

3.4 Patient Population

Patients receiving care at severe asthma secondary and tertiary care centres in each participating country in accordance with local regulatory/ethical requirements. The target is to enrol on average 2000 new patients into the ISAR globally per year with support from the core funding. Additional recruitment will be encouraged, but any support for this will be subject to availability of additional or self-funding within countries. The objective is to balance recruitment across the different countries. It is predicted that a minimum of 60% of the patients enrolled will be retained for annual follow-ups after adjusting for attrition, within each participating country.

Appropriate informed consent will be obtained from the patients to allow data sharing for ethical and REG (ADEPT) approved research. The anonymised Data Ethics & Protocol Transparency (ADEPT) Committee is commissioned by REG and its role is to review and approve the scientific merit of research proposals (http://effectivenessevaluation.org/adept-committee/). The committee's aim is to ensure database research is clinically appropriate and continues to bring genuine value to patients, public health and healthcare.

At enrolment and thereafter (at least) annually, patients will receive a complete asthma review in line with the standard data collection fields/codes set by the ISAR Delphi panel and agreed to by all participating countries as follows:

- Patient demographics
- Asthma history including prior exacerbations, allergic status, and current asthma control
- Important comorbidities including eczema, chronic rhinitis and allergic rhinitis and nasal polyps
- Asthma medications, including adherence data, where available
- Patient-reported outcomes including asthma control status (e.g. GINA-control), quality of life, and occupational history

- Spirometry
- Biomarkers (blood eosinophils, IgE, and FeNO where possible)
- Side effects related to steroid exposure (17) and biologics.

Data from these evaluations will be entered into a locally held registry then imported according to the ISAR Data Management Plan. Data of severe asthma patients already recorded in any existing registries may also be included. For consistency, any existing data will be aligned to meet the standard data collection fields/codes set by the ISAR Steering Group.

3.5 Inclusion Criteria

- Patients 18 years or older
- Patients in receiving treatment according to GINA Step 5 or uncontrolled in Step 4. Uncontrolled is defined as having severe asthma symptoms[1] or frequent exacerbations[2].

Patient Inclusion SOP will be provided to countries to help determine eligibility for ISAR.

3.6 Registry Follow-up

Due to the real-life nature of a registry, there will be no attempt to interfere with the routine clinical care of the patient and follow-up visit number per patient is conditional to his or her own health care utilization level. It is projected that a patient will encounter a secondary or tertiary clinic at least once a year. Specific variables from the Core and the Research variable list will be required from follow-up visits [post baseline (first visit during the data collection time-frame)] on eCRFs.

3.7 Consent Procedures

Subjects will be offered two levels of consent. Subjects will be asked to enter the registry for research purposes. An additional level of consent will allow future contact [for further follow-up/for invitation to participate in additional research studies]. Additionally, patient and legal guardian contact information will be collected at the site to facilitate future contact (not shared with ISAR OPC team).

4.0 DATABASE

[1] **Severe asthma symptoms (ERS/ATS Guidelines) (**Error! Reference source not found.**:**
(a) Poor symptom control where Asthma Control Questionnaire consistently >1.5, Asthma Control Test <20 (or "not well controlled" by NAEPP/GINA guidelines)
(b) Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)
(c) Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year

[2] **Frequent severe asthma exacerbations (ERS/ATS Guidelines) (**Error! Reference source not found.**:**
Two or more bursts of systemic corticosteroids (>3 days course each) in the previous year

4.1 Data Acquisition

A Memorandum of Understanding (MOU) and Data Sharing Agreement (DSA) with each country will govern the:

- The method of transmission and storage of data
- Data security and compliance with OPC data security standards
- The list of core variables required to extract from each country-specific database
- Oversight that resides with OPC to ensure confidentiality of data received
- Remote retrieval and appraisal of data from each country to be conducted by OPC

The Data Transfer SOP will be provided to each country to help anonymise and safely transfer data.

4.2 Data Management

A separate data management plan delineates all functions, processes, and specifications for data collection, extraction, delivery, cleaning and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. This will minimize common data entry errors. Concurrent manual data validation processes will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the Electronic Data Capture (EDC) system and followed up for resolution.

High data quality standards will be maintained, and processes and procedures utilised to repeatedly ensure that the data are as accurate as possible when presented for analysis.

Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data. All the modifications to the data will be recorded in an audit log. All data transfers and disputes will be shared and documented in the Country and ISAR Central Data Manger logs.

4.3 Registry Coding

The ISAR Steering Committee of leading experts will be coordinated by the REG. The group will agree on the standardised set of Core and Research data points and will hold regular meetings in order to ensure continued expert input throughout the development, expansion of the registry and research objectives are achieved.

All data collected by participating countries must comply with the standardised clinical codes and terms in the **S**ystematized **No**menclature of **Med**icine **C**linical **T**erms (SNOMED CT) dictionary which is becoming the recognised clinical successor to ICD and Read coding that can provide the level of detail required for the coding purposes of the registry. Ideally the data coding should be consistent with other medical coding systems used in clinical practice to avoid duplication. Standardised coding across the countries can be achieved by:

1. Setting up a local registry using the ISAR Core Variable CRF and EDC platform

2. Collecting or extracting data from existing registries using the current clinical coding system and ensuring that all Core Variables can be mapped to SNOMED CT code (conducted at OPC Global), or
3. Entering data into the country-specific ISAR registry using SNOMED CT code

SNOMED CT has been developed by the International Health Terminology Standards Development Organisation (IHTSDO), and is currently available in English and Spanish versions. There are also additional translations of SNOMED CT which are managed by Member countries. These versions have been created according to the IHTSDO translation principles and access to these translations can be retrieved through the relevant National Release Centre. SNOMED CT coverage includes clinical findings, symptoms, diagnoses, procedures, body structures, organisms and other aetiologies, substances, pharmaceuticals, devices and specimens. It can cross-map to other international standards and classifications (such as the International Classification of Diseases) facilitating data reuse to report statistical and management data using other code systems and interoperability amongst international terminologies, classifications and code systems.

Response options in the registry will be provided as radio buttons or dropdown menus, as appropriate, to eliminate data entry errors.

4.4 Registry Variables:

The ISAR will comprise two levels of standardised data collection, as described below

- Core Variable List (determined by a DELPHI Process): this will be made up of approximately 100 core variables and these will become mandatory and the minimal data to be collected by any country wishing to contribute data to ISAR.

- Research Variable List: This will be made up of all variables deemed useful for scientific research and maximal data collection and will become the ISAR optimal variable list. Extended variables will be collected via standardized bolt-on modules. To name a few: quality of life (Euro-QoL-5D and AQLQ), asthma control (ACQ7, ACT), Occupational History Questionnaire, Comorbidities, Vaccination History and Severe Asthma Biomarkers.

Please refer to appendix 7.1 for latest Core Variable List that resulted from the completion of round one and two of the DELPHI process. Additional variables may be added during the third round of the DELPHI process. It is recognised that the list might be subject to updates (for example after the conclusion of the DELPHI process, projected date of completion: May 2017).

4.5 The DELPHI Process

The Delphi process is an iterative method of questioning that works on the assumption that group judgments are more valid than individual judgments (18). After each round of questions, a Delphi administrator provides an anonymous summary of the experts' views from the previous round. As the process progresses, it is expected that the range of responses will decrease and the group will converge towards an agreed answer. An advantage of the Delphi process over other forecasting tools is that the anonymity of the participants ensures that all opinions are considered equally, enabling views to be changed without inhibition by participants.

Previous Delphi consensus studies in asthma and chronic obstructive pulmonary disease indicate that a panel consisting of at least 12 members is sufficient to generate a meaningful consensus. The DELPHI panel will bring together experts globally and each member will have at least one of the following:

1. A proven track record of relevant asthma research published in high-ranking peer reviewed journals;
2. History of participation in the development of databases and involvement with peer-reviewed journals and scientific congress committees; and/or
3. A commitment to advancing asthma management in clinical practice and expertise in data standards and data development.

Panel members identified are detailed below, further members may be added through a peer-nominated recruitment process that will be completed by May 2017:

Delphi Group Member	**Country**
David Price (chair/neutral facilitator)	Singapore
Liam Heaney	UK
Andrew Menzies-Gow	UK
Giorgio Walter Canonica	Italy
Eric Van Ganse	France
Manon Belhassen	France
Roland Buhl	Germany
Anke-Hilse Maitland- van der Zee	Netherlands
Leif Bjermer	Sweden
Peter Gibson	Australia
Vibeke Backer	Denmark
Celeste Porsbjerg	Denmark
Chin Kook Rhee	South Korea
Nikos Papadopoulos	Greece
Lauri Lehtimaki	Finland
Mark Fitzgerald	Canada
Luis Perez de Llano	Spain

Francisco de Borja Garcia-Cosio Piqueras	Spain
Guy Brusselle	Belgium
Loo Chian Min	Singapore
Sven Erik Dahlen	Sweden
Mark Hew	Australia
Matthew Peters	Australia
Erin Harvey	Australia
Katia M C Verhamme	Netherlands
Job van Boven	Germany
Mohsen Sadatsafavi	Canada
Elizabeth Bel	Netherlands
Ratko Djukanovic	UK

Delphi Process for Core Variables

- *Objective 1:* Obtain expert consensus on a list of core variables for the International Severe Asthma Registry (ISAR).
- *Objective 2:* Publish the finalised Core Variables.
- *Completion timeframe:* May 2017

The ISAR Delphi process will comprise of three rounds to gather anonymized opinions on the core variables electronically using an excel workbook (*The ISAR Delphi Core Variable Workbook)*.

Core Variables are data elements that will be collected from all countries into the central ISAR registry. Additional Variables are research variables found in the British and Australian registry, these can be reviewed by each member in order to suggest additional variables to the Core Variable List. Each country is allowed to keep any number of these Additional Variables as Extended Variables in the local registry/database.

Delphi Round 1

Step 1

- A variable workbook (*The ISAR Delphi Core Variable Workbook Round 1*) with the consolidated British and Australian registry variable list.
- The workbook will be sent to each DELPHI member electronically with the option to choose if a list of variables should be kept as core variables ('Core Variable List' worksheet).
- Each member is also allowed to suggest additional core variables from the 'Additional Variable List.' Alternative variables may be selected to add to the Additional Variable List

or even the Core Variable List. However, for each additional variable suggested for the core list one variable must be suggested for removal.

- Expert panel members will independently complete the workbook and send it via email back to the DELPHI central coordinator (Lakmini Bulathsinhala at lakmini@optimumpatientcare.org).

Step 2

- The Delphi central administrator will combine all workbooks and consensus on variables is evaluated by summary statistics (database type frequency counts) using a statistical program (e.g. SAS/Stata).
- An agreement on a variable of 66.6% will be considered a consensus.
- If a variable has above 50% but below 66.6%, the chair can delegate and imply consensus on the variable, therefore keep as a core variable or keep as a variable without consensus.
- The independent facilitator will present the summary statistics to the ISAR steering committee and Delphi committee.

Outcome

1. Variables with consensus will constitute as core ISAR data fields.
2. Variables that did not receive a consensus will be enumerated on a *The ISAR Delphi Core Variable Workbook Round* 2.

Delphi Round 2

- A second round of Delphi review for the remaining variables will be conducted and step 1 and 2 from Delphi Round 1 will be repeated.

Outcome

1. Variables with consensus will constitute as core ISAR data fields
2. Variables that did not receive a consensus will be enumerated on a *The ISAR Delphi Core Variable Workbook Round 3.*

Delphi Round 3

- A third round of Delphi review for the remaining variables will be conducted and step 1 and 2 from Delphi Round 1 will be repeated.

Outcome

1. Variables with consensus will constitute as core ISAR data fields
2. Any remaining variables without consensus can be reviewed another round at the discretion of the chair/neutral facilitator.

4.6 Electronic Data Capture

All new data will be entered directly into an EDC system. Both new and existing data platforms would be mapped and imported to a central data warehouse where the data would be held with a unique patient Identification Number (ID) but stored in a pseudonymised way.

All participating sites will have access to the data entered for patients enrolled at their site. All sites will be fully trained on using the available on-line data capture system, including eCRF completion guidelines and help files. Sites will be responsible for extracting batches of patient data for a specific data collection time frame. OPC will be responsible for importing and integrating into the central ISAR data repository. Physicians and data entry personnel will be able to access their account with a username and password. All eCRFs should be completed by designated, trained personnel or the coordinator, as appropriate. All changes or corrections to eCRFs should be documented in an audit log, with adequate explanation to support the data changes.

For all existing registries or local registries using a unique EDC system, sites will be responsible for extracting batches of patient data for a specific data collection time frame. OPC will be responsible for safely transporting and importing each batch into the central ISAR data repository where data regulations within a country allows for it.

4.7 Data Ownership

Each participating country will own their country-specific data. However, in joining the ISAR network, all participating countries as a minimum, must agree to allow output data from their respective registries for collaborative independent research recommended by the ISAR Steering Committee and approved by ADEPT. The ADEPT committee's aim is to ensure database research is clinically appropriate and continues to bring genuine value to patients, public health and healthcare. The extraction and integration of datasets for ethically approved research studies will be managed by OPC. The core funding allows for one complete global research project per year and in addition the creation of four additional data sets for academic research. To maximise dissemination of the research, medical writing expertise will be funded to deliver four abstracts and two manuscripts annually.

4.8 Data Access & Governance

Scientific Governance: The regulation of the registry will be under the jurisdiction of the ISAR committee. The ISAR committee will determine the scientific and research merits of any research proposal to access and/or use anonymous data from ISAR.

Ethical Governance: Valid applications approved by the ISAR Steering Committee will go through ADEPT review for ethics and governance approval. The ADEPT committee will provide ethical governance of the data. ADEPT is a governance committee commissioned by REG to provide governance and regulation for existing large anonymous databases including the International

Helping Asthma in Real-life Patients Database (iHARP Database), and the Optimum Patient Care Research Database (OPCRD). The application will require the applicant to provide the following:

- An Anonymised Data Ethics & Protocol Transparency (ADEPT)
- Protocol
- Ethics/Regulatory approvals (if applicable)
- Data specifications/requirements
- Application fees

As per common practice for large anonymous databases and registries, applications can have one of the following outcomes:

- Rejection
- Re-submission with Amendment
- Conditional Approval
- Full Approval

The ADEPT committee will grant access to the central ISAR database. It is mandatory for proposals requiring access and use of ISAR data to submit an application to the ADEPT Secretariat.

Data Procurement: Upon receipt of governance approval, OPC will transfer anonymous data by way of a dataset from the central ISAR database according to the Data Sharing and User Agreement. This agreement will delineate the data specifications/requirements approved by ADEPT.

5.0 RESEARCH

Research questions will be gathered from the ISC and prioritised during the annual steering committee meeting at REG Summit.

5.1 Research ethical approval and access

Each participating country will own their country-specific data. However, in joining the ISAR network, all participating countries as a minimum, must agree to allow output data from their respective registries for collaborative independent research recommended by the ISAR Steering Committee and approved by Anonymised Data Ethics & Protocol Transparency (ADEPT). The ADEPT committee's aim is to ensure database research is clinically appropriate and continues to bring genuine value to patients, public health and healthcare.

5.2 Research Dissemination

The core funding allows for one complete global research project per year as well as the creation of 4 additional data sets per year from 2017 for academic research by registry members in the

participating countries. Two abstracts will be submitted per year from 2017 until 2021 as well as 2 manuscripts for core activities in 2017 and 1 per year thereafter for core research interests. Additionally, 4 posters for core activities will be prepared for presentation in 2017 and 2 every year thereafter. Furthermore, approximately an additional 2 abstracts and 2 manuscripts per year for non-core research activities will be generated in 2018 until 2021.

The existing ISAR funding arrangement makes provisions for data access for the following research work and initiatives to be undertaken by the ISAR collaborative group following the establishment of the registry:

- 1 Core Research Project per year
- 4 Academic Datasets per year

5.3 Funded Research

The research for funded projects must be for academic purposes and can be proposed by any member of the ISAR collaboration. The research projects chosen for funding requires ISC prioritisation and ADEPT approval. Current funding covers:

5.3.1 One Core Research Project Annually

1 Core research project per year for the current funding duration (2017*–2021) is fully funded for the ISAR Steering Committee. This specifically refers to the following components:

- **Protocol:** documented overview of a proposed study as designed in relation to its objectives and research questions. This would include study background, research objectives, study design, methodology etc.

- **Data Procurement:** developing systems and processes to facilitate the collection of standardised data variables from individual patients, sites and countries to contribute to the ISAR registry.

- **Dataset Creation:** a specific sub-set of the registry data (data-set) created as per the data specification set out in a given research proposal/protocol as approved by the ISC and ADEPT.

- **Data/Statistical Analysis:** examination summarization, manipulation, and interpretation of the dataset to answer any approved research question/protocol – e.g. discovering underlying causes, patterns, relationships, and trends.

- **Study Report:** communicating the results of approved research studies, and the conclusions that can be drawn from them, including the methodology used, the data collected and statistical results drawn from that data.

- **Publication:** distributes research results to the wider community via peer reviewed journals and international conferences (abstracts and posters). This is intended to further the progress of science in any given research field.

5.3.2 Academic Datasets Annually

Funding for 4 academic datasets for the ISAR Steering Committee has been provided under the current funding duration (2017*–2021). This specifically refers to the following components:

- **Data Procurement:** developing systems and processes to facilitate the collection of standardised anonymous data variables from individual patients, sites and countries to contribute to ISAR.

- **Dataset Creation:** a specific sub-set of the registry data (data-set) created as per the data specification set out in a given research proposal/protocol as approved by the ISC and ADEPT.

6.0 DISSEMINATION & COMMUNICATION

6.1 Publication Plan

Manuscript and abstract drafts will be delivered to ISAR steering committee and qualified authors, then first round of revisions, repeat review and revisions will be conducted. A final draft will be shared with all authors for approval and to submit to a journal identified by the authors and/or the steering committee. A copy of all peer-reviewed publications will be submitted to the ADEPT Secretariat. Post publication public relation articles will be based on data released in public meetings or publishable updates found in the wider web. For more detailed information on publication can be found in the ISAR publication charter.

6.2 Conferences

Any research findings (UK-specific and/or pooled international findings) from the ISAR registry will be submitted in abstract form to key respiratory congresses (e.g. the European Respiratory Society [ERS] Annual Congress, the American Thoracic Society [ATS] Annual Congress).

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7.1 APPENDIX: Core Variables

	Category	Variable Field Name	Response Options (where applicable)
1	Inclusion Criteria	Does the patient have uncontrolled asthma and on more than moderate amounts of ICS? Please check one of the following: 1. On GINA Step 5 2. (a)Uncontrolled on GINA Step 4: Has exacerbations requiring OCS 2. (b) Uncontrolled on GINA Step 4: Has Severe asthma symptoms	No/Yes
2	Inclusion Criteria	Patient fulfils the inclusion criteria for ISAR	No/Yes
3	Patient details	Date of visit	DD/MM/YYYY
4	Patient details	Date of Birth Age at Assessment	DD/MM/YYYY Number (auto-calculated)
5	Patient details	Age at Assessment	Number (auto-calculated)
6	Patient details	Gender	Female/Male
7	Patient details	Ethnicity	Caucasian/South East Asian/North East Asian/African/Mixed/Other
8	Patient details	BSA	Decimal number (auto-calculated)
9	Patient details	BMI	Decimal number (auto-calculated)
10	Patient details	Height	Decimal Number
11	Patient details	Weight	Decimal Number
12	Patient details	Has the patient had Bronchial thermoplasty?	No/Yes
13	Occupation	What is the current occupation of the patient?	Free Text
14	Medical History	What is the current smoking status of the patient?	Never smoked/Ex-smoker/Current smoker

15	Medical History	Pack years	Number (auto-calculated)
16	Medical History	-Years since last smoked? (Please indicate the time frame from which the patient had stopped smoking)	Number
17	Medical History	At what age did the patient's asthma symptoms begin? Whole years or months if < 1 year	Number
18	Medical History	Number of exacerbations requiring rescue steroids in the past 12 months?	Number
19	Medical History	Total number of episodes of invasive ventilation ever?	Number
20	Medical History	Total number of A&E attendances for asthma in the past 12 months?	Number
21	Medical History	Total number of hospital admissions for asthma in the past 12 months?	Number
22	Relevant Comorbidity	Indication of: Eczema	Never/Past/Current
23	Relevant Comorbidity	Indication of: Allergic Rhinitis	Never/Past/Current
24	Relevant Comorbidity	Indication of: Chronic Rhinosinusitis	Never/Past/Current
25	Relevant Comorbidity	Indication of: Nasal Polyps	Never/Past/Current
26	Relevant Comorbidity	Indication of Atopic Disease Yes, if indicated for Eczema Yes, if indicated for Allergic Rhinitis	No/Yes (Auto-populated)
27	Blood/Sputum	What is the Highest Blood Eosinophil Count (within the past year)?	Decimal Number
28	Blood/Sputum	-Date of highest blood Eosinophil count (within the past year)	DD/MM/YYYY
29	Blood/Sputum	-Was this highest blood Eosinophil count during an exacerbation event?	No/Yes
30	Blood/Sputum	+What is the Highest Blood Eosinophil Count?	Decimal Number

		(within the past year and not during exacerbation)	
31	Blood/Sputum	+Date of highest blood Eosinophil count (within the past year and not during exacerbation)	DD/MM/YYYY
32	Blood/Sputum	What is the Current Blood Eosinophil Count (latest)?	Decimal Number
33	Blood/Sputum	-Date of current Blood Eosinophil count (latest)	DD/MM/YYYY
34	Blood/Sputum	What is the Highest Sputum Eosinophil Count (within the past year) (Percentage)	Decimal Number
35	Blood/Sputum	-Date of highest sputum eosinophil count (within the past year)	DD/MM/YYYY
36	Blood/Sputum	What is the IgE Count (latest)	Decimal Number
37	Diagnostics	Was CT Scan (Chest) performed?	Normal/Abnormal/Not done
38	Diagnostics	-Date of CT Scan (Chest)	DD/MM/YYYY
39	Diagnostics	Was Bone Densitometry (DEXA) performed?	No/Yes
40	Diagnostics	-Date of Bone Densitometry (DEXA)	DD/MM/YYYY
41	Lung Function	Pre-bronchodilator FEV1	Decimal Number
42	Lung Function	Post-bronchodilator FEV1	Decimal Number
43	Lung Function	Pre-bronchodilator FVC	Decimal Number
44	Lung Function	Post-bronchodilator FVC	Decimal Number
45	Lung Function	Predicted FEV1	Decimal number (auto-calculated)
46	Lung Function	Pre-bronchodilator FEV1 (% predicted)	Decimal number (auto-calculated)
47	Lung Function	Post-bronchodilator FEV1 (% predicted)	Decimal number (auto-calculated)
48	Lung Function	Predicted FVC	Decimal number (auto-calculated)
49	Lung Function	Pre-bronchodilator FVC (% predicted)	Decimal number (auto-calculated)
50	Lung Function	Post-bronchodilator FVC (% predicted)	Decimal number (auto-calculated)
51	Lung Function	FEV1/FVC ratio pre-bronchodilator (%)	Decimal number (auto-calculated)

52	Lung Function	FEV1/FVC ratio post-bronchodilator (%)	Decimal number (auto-calculated)
53	Lung Function	Was the PC20 methacholine/histamine test performed?	No/Yes
54	Lung Function	-Date of PC20 test	DD/MM/YYYY
55	Lung Function	-PC20 methacholine/histamine Test result	Decimal Number
56	Lung Function	Was the Fractional Exhaled Nitric Oxide Test performed?	No/Yes
57	Lung Function	-Date of Fractional Exhaled Nitric Oxide test	DD/MM/YYYY
58	Lung Function	-Fractional Exhaled Nitric Oxide test result	Decimal Number
59	Allergen Testing (ALL)	Was an Environmental Allergen Test conducted?	Serum Allergen Test (CAP, ELISA, RAST) /SPT/Not Done
60	Allergen Testing (RAST)	-Positive to perennial allergen (Serum Allergen Test)?	No/Yes
61	Allergen Testing (RAST)	+Specify perennial allergen(Serum Allergen Test (Select all that apply)	Dust Mite (e.g. D.Pteronyssinus)/Grass mix/Cat hair/Mould mix/Dog hair/Aspergillus/Other(Please Specify)
62	Allergen Testing (SPT)	-Positive to perennial allergen(SPT)?	No/Yes
63	Allergen Testing (SPT)	+Specify perennial allergen(SPT) (Select all that apply)	Grass Mix/Weed Mix/ Mould Mix/ Dust Mite/ Cat/Dog/ Trees/ Aspergillus/ Food Mix/ Animal Mix/ Other (Please specify)
64	Asthma Control	Day time symptoms? (more than twice per week)	No/Yes
65	Asthma Control	Any activity limitation?	No/Yes
66	Asthma Control	Any nocturnal symptoms/awakening?	No/Yes
67	Asthma Control	Reliever medication use? (more than twice per week)	No/Yes
68	Asthma Control	Is Lung function (PEF or FEV1) < 80% of predicted or personal best (if known)?	No/Yes

69	Asthma medication	Is the patient prescribed Maintenance Oral Steroids?	No/Yes
70	Asthma medication	-Start Date of Maintenance Oral Steroids	DD/MM/YYYY
71	Asthma medication	Is the patient on a prescription for ICS+LABA combination therapy? (Please select from list)	No Budesonide+ Formoterol Fluticasone Furoate + Vilanterol Fluticasone propionate + Salmeterol Fluticasone propionate + Formoterol Mometasone + Formoterol Beclomethasone + Formoterol Other
72	Asthma medication	-Start Date of ICS+LABA combination therapy?	DD/MM/YYYY
73	Asthma medication	Is the patient on a prescription for ICS (only)? (Please select from list)	No Triamcinolone Acetonide Mometosone Furoate Fluticasone Propionate Fluticasone Furoate Ciclesonide Flunisonide Budesonide Beclomethasone Other
74	Asthma medication	-Start Date of ICS?	DD/MM/YYYY
75	Asthma medication	Is the patient on a prescription for LABA (only)? (Please select from list)	No Formoterol Salmeterol Indacaterol Arformoterol Olodaterol Other
76	Asthma medication	-Start Date of LABA?	DD/MM/YYYY
77	Asthma medication	Is the patient on a prescription for LAMA? (Please select from list)	No Aclidinium Tiotropium Umeclidinium Glycopyrronium Other
78	Asthma medication	-Start Date of LAMA?	DD/MM/YYYY

79	Asthma medication	Is the patient on a prescription for Theophyllines? (Please select from list)	No Theophylline AminoPhylline Other
80	Asthma medication	-Start Date of Theophylline?	DD/MM/YYYY
81	Asthma medication	Is the patient on a prescription for Leukotrine Receptor Antagonist(LTRA)? (Please select from list)	No Zafirlukast Monteleukast Other
82	Asthma medication	-Start Date of Leukotrine Receptor Antagonist(LTRA)?	DD/MM/YYYY
83	Asthma medication	Is the patient on a prescription for Anti-IgE Treatment? (Prescription for Omalizumab)	No/Yes
84	Asthma medication	-Start Date of Anti-IgE Treatment?	DD/MM/YYYY
85	Asthma medication	Is the patient on a prescription for Anti-Interleukin 5 (Anti-IL5) Treatment? (Please select from list)	No Reslizumab Mepolizumab New biologics (e.g: Benralizumab) Other (Other new biologics will be added once approved and in use)
86	Asthma medication	-Start Date of Anti-Interleukin 5 (Anti-IL5) Treatment?	DD/MM/YYYY
87	Asthma medication	Is the patient on a prescription for Macrolide Antibiotic Treatment? (Please select from list)	No Azithromycin Clarithromycin Erythromycin Roxithromycin Fidaxomicin Telithromycin Other
88	Asthma medication	-Start Date of Macrolide Antibiotic Treatment?	DD/MM/YYYY
89	Asthma medication	Is the patient prescribed other steroid sparing agents?	Free Text
90	Adherence	Is there evidence of poor adherence?	No Yes: Clinical impression Yes: Objective Measures Yes: Prescription Records

91	Management Plan	Are there any <u>other</u> factors contributing to severe asthma symptoms?	Free Text
92	Management Plan	What is the current Clinical Management Plan? (Select all that apply)	Discharge to local service Optimisation of current treatment Biologic therapy *(Specific drug can be found in current medication)* Bronchial thermoplasty Maintenance oral corticosteroids Steroid sparing agent *(Specific drug can be found in current medication)* Enter into clinical trial Other (please specify)