REG
Respiratory Effectiveness Group

ADVANCES

in Real-life Respiratory Research

The Respiratory Effectiveness Group Newsletter
ISSUE October 2021

www.regresearchnetwork.org

THE RESPIRATORY EFFECTIVENESS GROUP NEWSLETTER

ISSUE OCTOBER 2021

THE REG BOARD OF DIRECTORS

Sinthia Bosnic-Anticevich
President

Nikos Papadopoulos
Past President

Dermot Ryan
Vice President for Finances and Supporter Relationships

Walter G Canonica
Vice President for Global Collaboration

Nicolas Roche
Vice President for Methodology

Antonio Anzueto
Vice President for Internal Organisation

Omar Usmani
Vice President for Scientific Outputs

Alan Kaplan
Vice President for Events

Joan B Soriano

Marc Miravitlles

OVERSIGHT COMMITTEE

Nick May

Trevor Lambert

Keith Allan

CEO AND SUPPORTER LIAISON

Michael Walker

SCIENTIFIC RESEARCHERS

Graham Lough

Sarah Lucas

FINANCIAL MANAGEMENT

Victoria Cooper
Red Shoes Accounting

CONTENTS

REG Respiratory Effectiveness Group

enquiries@regreseachnetwork.org

@RespirEffect

Respiratory Effectiveness Group

www.regresearchnetwork.org

COPYRIGHT © 2021 Respiratory Effectiveness Group

EDITORIAL

Sinthia Bosnic-Anticevich
REG President

DEAR COLLEAGUES,

It is great to have the opportunity to write to you as we resurface, after 18+ months of the pandemic and over 3 months in lockdown (no doubt you have heard about the strictest of 'stay at home orders' in Australia). So at this time, it is impossible not to reflect and I cannot help but wonder, what next..

While it has been wonderful that our global conferences and meetings have continued through virtual platforms, often shortened but certainly remaining high quality; I do reminisce of what we have missed. I have missed the real-life engagement, the face-to-face discussions, and the social catch-ups over a coffee or a drink. And after a couple of decades working as a real-world researcher, I can say that these face-to-face encounters were fundamental to my enjoyment of my work and to the generation of new ideas. Therefore, like many, I personally am delighted that face-to-face is coming back.

But what will this new face-to-face look like? Will we still travel halfway around the world to meet for a few hours or will we continue to meet virtually? Will the cost savings associated with virtual meetings outweigh the benefits of face-to-face interactions. Does the ability to be anywhere in the world at anytime, virtually, mean that there are new opportunities open to many more individuals? And at what personal or professional cost does working both day and night, in order to be on the same time zone as 3 other continents have on our wellbeing and long term productivity. Do we know the answer to these questions, and do we have the means to find them?

The answer of course is "yes". We have the real work evidence that can answer all of these questions and I believe we should seek out the answers. We have the opportunity to better understand the impact of the way in which we work, and move and we should do what we promote – use real work evidence to determine what we do next. I guess if one thing is certain, what the past 20 months have highlighted is the importance of real work evidence, the need to look at it over time and the high relevance of it to those who need to make decisions that affect us all. Perhaps it is time now, not only to use it to improve the health and well being out patients, but to get guidance on what and how we do things better as a community of real-world researchers and clinicians.

Stay safe, be happy and I look forward to seeing you at the 2022 REG Summit.

Sinthia Bosnic-Anticevich
Professor
Woolcock Insitute of Medical Research
University of Sydney, Sydney, Australia

REG TEAM UPDATE

Michael Walker
REG CEO

As the global pandemic has continued, the rollout of vaccinations brings new hope that we will be able to return to many of the ways of life we enjoyed before. REG has adapted to the situation and our work continues.

Our REG projects are progressing well, despite the ups and downs of the pandemic. An international Impact of Inhaler Choice on Personalised Healthcare & the Environment is currently running, as is recruitment in a multinational multicentre project in peak inspiratory flow. A more detailed update of these activities can be found later in this issue. If you would like to know more about these or any of our other projects, please contact REG at enquiries@regresearch-network.org

Many of the Working Groups have held virtual meetings in place of the face to face meetings during this year with good discussions and progress made. The Working Group calls are an important opportunity for our Working Group members to connect and continue our active projects or discuss new projects in development. In 2022, we plan for the return of face-to-face meetings.

REG is excited to announce that the REG Summit 2022 will be a live event and is planned for 17th to 19th March 2022. We invite everyone to join the meeting and re-acquaint yourself with colleagues and friends. The Summit will be a stimulating scientific programme providing participants with opportunities for Q & A and discussions about the many issues and controversies that challenge everyday care of patients. Importantly, the data and discussions will also focus on the pandemic and what we have learnt. Live Working Group meetings will also be held in conjunction with the REG Summit.

I would like to acknowledge the support from our long-term supporters. Without their ongoing collaboration a lot of the work of REG would not be possible. I hope others are encouraged by the activities of REG and the REG Working Group meetings and will collaborate with us later this year or plan to in 2022. We will continue to support and reach out to our partners as we work together in real-life research.

REG

REG SUMMIT 2021 VIRTUAL

INTRODUCTION

REG Summit 2021 took place online from 18th to 20th March. The summit consisted of 8 exciting sessions on a wide and diverse range of key issues and topics in respiratory health, each featuring talks and debates from a selection of esteemed speakers and guests. Each of these sessions are summarised below.

SESSION 1 COVID-19

Prof. Antonio Anzueto chaired the timely session on COVID-19.

Prof. David Halpin spoke about the risks and management strategies for COVID-19 and chronic respiratory disease (CRD). Prof. Haplin discussed that patients with COPD, CRD, comorbidities and who are active smokers do not have a greater risk of testing positive for COVID-19, but it may reflect the effect of protective strategies. Similarly, this cohort of patients are also not at significantly greater risk in hospitalisation or ICU admission. However, they may be at a slightly increased risk of developing severe disease and death if they have COVID-19. In particular, patients over the age of 70 with underlying lung disease may have moderately increased risk of developing long COVID, i.e., symptoms persisting for longer than 28 days. Prof. Haplin advised that COPD patients should still be treated with ICS as there is no evidence of increased risk of harm and still potentially some benefit. He concluded that there is no evidence to suggest that management of COPD patients infected with COVID-19 should differ from those not infected.

Next, Prof. Tobias Welte spoke about COVID-19 and the future, in terms of what we need to do, with and without a vaccine. He highlighted that vaccination is the only option to get out of permanent lockdown as vaccines offer effective protection against common COVID-19 variants and adaptation of vaccines to new variants is possible too. However, Prof. Welte stated that the current treatment options for COVID-19 are limited. There are only a number of promising results out of Phase II studies reported. Therefore, there is urgency for regulatory authorities to approve new treatment options to make public funding available for drug development.

SESSION **2** Environment and Lung Health

In session 2, Prof. Joan B. Soriano chaired this excellent session which covered climate change, inhaler choice and E-cigarettes.

First, Prof. Josep M. Anto began his sobering talk by stressing the uncertainty surrounding the impact climate change on respiratory health, and the different direct and indirect pathways that could affect health. He concluded that policy developers should aim to develop policies which are beneficial to both planetary health and human health.

Next, Dr Omar Usmani gave a spirited talk on inhaler choice and the effect of policy on personalised healthcare balanced with the global warming potential of inhalers, providing evidence of patient preference and improved outcomes using pMDIs over DPIs. Dr Usmani concluded with a message from the ACT initiative: prescribers of inhalers should assess what is best suited for their patient, choose the appropriate inhaler and provide device training.

Finally, in the first pro-con debate of the Summit, both Dr Alan Kaplan and Prof. Antonio Anzueto gave spirited arguments for and against, respectively, E-cigarettes as a valuable aid to smoking cessation in a thrilling debate. Dr Kaplan argued that anything that aids smoking cessation should be utilised. He highlighted that E-cigarettes outperform nicotine replacement theory in smoking cessation and were 95% safer than cigarettes. Prof. Anzueto countered by arguing that E-cigarettes could normalise smoking and are attractive to teenagers. He added that the ingredients in E-cigarettes contain harmful additives and are developed by tobacco companies to encourage smoking and develop nicotine addiction.

Dr Kaplan emerged victorious, receiving 71% of votes for E-cigarettes being used to aid smoking cessation.

SESSION **3** Current questions in asthma management

This session was fortunate enough to have two chairs:
Prof. Alberto Papi & Prof. Giorgio Walter Cannica.

Dr Nick Hanania discussed factors to consider when choosing a biologic treatment for patients with high T2 severe asthma. He also presented some of the available tools to aid selection of biologics and highlighted the large number of unmet needs. The subsequent discussion centred around further unmet needs including improved measures of quality of life, real-world data to better understand long-term safety and impact of biologics and non-T2 asthma.

In the session's pro-con debate, Prof. Helen Reddel argued that while low dose ICS/formoterol combination should not always be the reliver of choice it should be given a higher preference. Combination ICS/formoterol in mild to moderate asthma reduces exacerbations, OCS use and provides similar symptom control to SABA alone. She highlighted safety concerns with the use of SABA, as even moderate SABA use is associated with increases in exacerbations. There is also a need to consider patient behaviour; starting patients on SABA alone, which give almost immediate symptom relief, trains them to consider SABA as their primary treatment. In his argument against the move to as required ICS/formoterol, **Dr Dermot Ryan** discussed the differences between highly controlled

clinical trials and vastly different situation in primary care, focusing on 2 main points 1) poor diagnosis, which could result people without asthma taking high dose ICS and 2) loss of lung function due to those on ICS/formoterol having insufficient ICS to prevent lung remodelling. He concluded that improved asthma care is needed, involving confirmed diagnosis, education, regular review, prescription monitoring and accredited asthma care services. The debate was won by **Prof. Reddel** with 67% of the vote.

SESSION 4 COPD: Treatment Controversies

Dr. Marc Miravitlles chaired the two debate sessions on the pros and cons on whether dual bronchodilators (LABA/LAMA) should be used to treat COPD, and on the pros and cons of whether triple therapy will reduce mortality.

The first pro-con debate of the session on whether LABA/LAMA should be started earlier began with **Prof. Bartolome Celli** supporting the early use of dual bronchodilators (LABA/LAMA) to treat COPD. He argued that bronchodilators are the cornerstone of COPD pharmacotherapy. Dual bronchodilators have a greater effect than single agents, with a similar potential risk of side effects. They are well tolerated at the right dose, and improve other outcomes, especially for those who do not respond to one single agent. He concluded that the earlier dual bronchodilator therapy is started, the better it is for the course of the disease.

Prof. Antonio Anzueto supported the use of only one bronchodilator in treating COPD. He contended that treatment can impact disease progression. LABA (Tiotropium) monotherapy can significantly improve lung function, decrease hyperinflation and impacts on patients' quality of life. A monotherapy bronchodilator has the same effect in reducing exacerbation risk similarly to a dual bronchodilator. He concluded that it would require clinical studies to prove that fixed LABA/LAMA combination should be first line treatment for COPD.

The audience voted 93% in favour of **Prof. Celli's** argument that dual bronchodilators should be used earlier in the treatment of COPD.

In the next pro-con debate, Prof. MeiLan K. Han supported that triple therapy reduces mortality. She used the Gordis Criteria for Causal Association to support this theory and all criteria were met. She sited that triple therapy reduces moderate-severe exacerbations and mortalities associated with exacerbation in a subset of patients. In comparison to dual bronchodilators, all three studies (IMPACT, ACM and ETHOS) showed lower mortality rate in patients who had triple therapy and had statically significant relative reduction in mortality risk. ETHOS also showed dose-response relationship where higher dose resulted in lower deaths. Annual risk reduction for patients who received triple therapy studies was much higher in comparison to standard therapies.

Prof. Anthony D'Urzo stated that there is not enough evidence that triple therapy reduces mortality. The ETHOS and IMPACT triple therapy studies have methodological limitations and correcting the factors may yield different conclusion. These studies are difficult to interpret due to statistical issues because they contain both addition and withdrawal medication arms, included patients with a past history of asthma which means they are either more likely to have severe exacerbation and / or were already on ICS-containing therapies. Prof. D'Urzo highlighted that the TORCH and SUMMIT studies rejected the benefits of ICS on the mortality in COPD. TORCH and SUMMIT have mortality rate as their primary endpoints,

excluded patients with a diagnosis of asthma and also had a longer duration that the ETHOS and IMPACT studies. TORCH and SUMMIT both resulted in a higher number of deaths and have failed to show a significant reduction in mortality.

This debate was a close one, but **Prof. Han** enjoyed a minor victory, winning just over half of the audience vote at 53% that use of triple therapy reduces mortality.

SESSION 5 Child Health

Prof. Adnan Custovic discussed data showing that asthma does not appear to be a risk factor for severe COVID-19 and may indeed be protective. He presented work by the REG PeARL think tank and others illustrating changes to asthma services during the pandemic, e.g. use of telemedicine, has not had a detrimental effect on asthma patients; in fact asthma control and outcomes have improved. The following discussion centred on the future potential of telemedicine, increased remote monitoring and for good environmental control to improve outcomes.

Prof. Sejal Saglani talked about the utility of sputum and bloods eosinophils and FeNO in paediatric asthma. While there is still much work to be done such as assessing cut-off values for blood eosinophil levels in children and determining biomarkers for non-eosinophilic asthma there is a need to place more emphasis on the use of biomarkers in clinical practice. Clinicians should be considering combinations of biomarkers and assessing biomarkers longitudinally in their patients.

In his presentation focused on differences between preschool children with asthma and older children and adults **Dr James Paton** discussed differences in asthma phenotype in young children and how although treatment is generally consistent across age groups there is less evidence to support the use of oral corticosteroids for asthma exacerbations in preschool children. He highlighted the importance of focusing not only on symptoms but asthma exacerbations as an outcome and the importance of treatable traits. It was raised in the discussion that there is a need rethink the strategy for managing exacerbations across all age groups perhaps investigating biologics in acute asthma exacerbations.

SESSION 6 ILD / IPF

Dr Mark Jones chaired this fascinating and topical session covering early diagnosis of ILD and ILD in the post-COVID era.

Dr Pilar Rivera Ortega outlined the tools for early diagnosis of IPF. Presenting evidence from multiple studies, she identified expert multi-disciplinary teams and new diagnostic biomarkers to aid early identification. She stressed that referral of a patient from primary care centres to a specialist ILD unit is the highest priority. She highlighted effective ways to achieve this: training of GPs to recognise ILD; social media and awareness; the need for national and international registries; and the creation of MDT experts who can provide virtual support at regional, national, and international levels.

Prof. Fernando Martinez first discussed the impact of COVID on patients with known ILD. He showed new evidence that COVID-infected patients with ILD, particularly IPF, have worse outcomes and higher mortality; and that lower lung function, age and obesity worsen effect of fibrosis. He also highlighted through comparison of COVID-infected patients with

ILD and without ILD the greater need for hospitalisation and reduced likelihood of discharge after hospitalisation in those with ILD. Next, Prof. Martinez discussed the long-term effects of COVID on fibrosis, providing evidence suggesting that most patients improve after COVID infection. However, he stated that COVID is associated with persistent symptoms, impaired lung function and CT abnormalities. He finally suggested that 3 months may be the critical time point to assess whether post-COVID fibrosis is progressive.

SESSION 7 Digital Health

Prof. Henry Chrystyn chaired the riveting session on digital health.

Prof. John Blakey spoke about the evidence for digital inhalers, more specifically what evidence do smart devices improve care and outcomes in airway disease. Digital inhalers have shown an increase in the total number of doses of preventer drug taken for people with airway disease shown across different age group, geographical locations and digital inhaler types. Studies showed that if doses are taken, they are usually taken on time. However, missing doses is a far greater issue than taking an extra dose. Patients who received tailored clinical feedback on their actual usage of their inhaler made fewer technique errors than those who receive intensive education, their critical errors are relatively common. Prof. Blakey concluded that more studies are required to ascertain that smart devices can improve care processes and outcomes in airway diseases long term.

Next, Prof. Job van Boven spoke about the health economics of digital technologies. The potential cost-effective subgroups where smart digital technologies would pay off from a payers' perspective are patients considered for step-up therapy (triple, oral corticosteroids, biologics), severe asthma (GINA-5) on biologics/OCS, patients with uncontrolled asthma/COPD (frequent exacerbations associated hospitalisation, high SABA use) and for patients whose starting novel therapy can use digital technology to form a habit in using it, to receive feedback while on therapy. He specified that, from a societal perspective, patients with asthma and COPD of working age would potentially benefit from using digital technology to reduce their management cost. These subgroup sizes and per patient costs should be assessed in accordance with the country, setting and payer's circumstances.

SESSION 8 Thresholds for Referral

The chair for the final session was Prof. Mike Thomas. He introduced the context of the session, that patients with illnesses like COPD, asthma and allergy are provided primary care but that treatment and management are sometimes only available in secondary care.

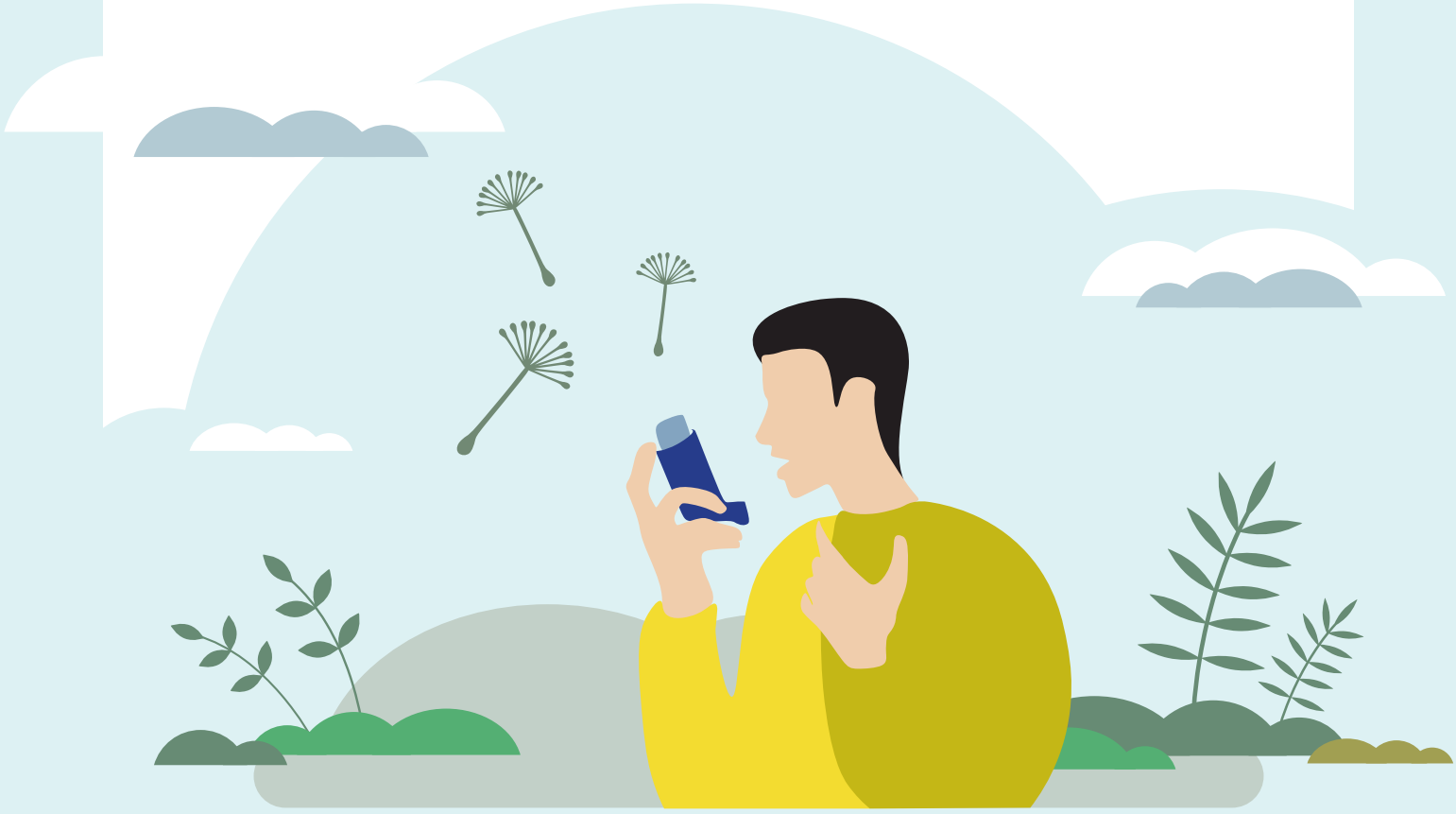
Dr Alan Kaplan presented the threshold for referral in asthma. He commented that there are currently no processes to alert specialists for patients who urgently need a referral, such as uncontrolled asthma patients on Step 2 therapy (overuse of SABA/LABA) and recurrent oral steroids. The IPCRG tool provided a list of things to be included in a referral letter – the criteria on which the diagnosis was made, duration of asthma, measures of current disease control, current treatments and their adherence, inhaler technique review, patients' understanding of their treatments, impact on quality of life, comorbidities and smoking behaviour. Communications between primary and secondary health care determines the

efficiency and effectiveness of the referral process. While primary care physicians wait for specialists to see their patients, they can potentially advise patients to do more respiratory tests such as spirometry, CBC, FeNO, CT chest scan, sputum eosinophils, allergy testing and IgE tests to provide the specialist with more information during their consultation.

Next, Prof. Todor Popov presented the threshold for referral in allergy. He remarked that there is a lack of allergy services across the world to adequately meet the high demand of allergy referrals. This is partly due to the inadequate primary care services which are affected by poor training of practitioners and poor access to specialists. On the other hand, secondary care services are affected by the lack of appropriately trained personnel and poor referral practices from primary care. The propensity of patients to seek care for their symptoms also varies across countries. Patients' seeking care behaviour is influenced by the care provided by the health care systems.

In the final talk of the day, Prof. Chin Kook Rhee presented on the threshold for referral in COPD. Criteria for outpatient COPD referral include experiencing symptoms despite using first line therapy, rapid decline in FEV1 (10% per year) and hypercapnia and/or hypoxia. The key time points for specialist referral is at diagnosis, at discharge following hospitalisation for an exacerbation and when symptoms are found to be progressively deteriorating. Prof Rhee then highlighted barriers to pulmonary rehabilitation referral and need for patient education to seek care at the appropriate time.

The REG Summit 2021 was a tremendous success and attracted a wide audience from around the world. Thanks to all the speakers and chairs of the sessions, as well as the support from our sponsors.



REG Respiratory Effectiveness Group

SAVE THE DATE

THE RESPIRATORY EFFECTIVENESS GROUP

REG SUMMIT 2022

Barcelona • SPAIN

LIVE

17-19 March 2022

www.regsummit2022.org

REG SUMMIT 2022 LIVE

LIVE, 17 – 19 March 2022

REG is pleased to announce the return of the REG Summit as a face-to-face live meeting. The meeting will be held in Barcelona and will bring together real-life research experts from around the world to discuss the latest findings and new areas for collaboration in their respective fields of real-life respiratory research.

The REG Summit is a well-known meeting of global respiratory key opinion leaders who actively conduct real-life research using and creating Real World Evidence. REG collaborators (researchers, clinicians, general practitioners and allied health professionals) have conducted numerous database projects as well as prospective pragmatic trials and continue to seek answers to the many complex issues faced by respiratory patients.

The REG Summit starts on Thursday 17th March with the REG Working Groups meeting to review progress on projects as well as developing new ideas and areas for further investigation. The scientific programme follows all day on Friday 18th and concludes at 13:00 on Saturday 19th March.

The scientific programme will include robust and informative discussions and debate on the latest thinking on treatment strategies and what are the needs to move the field forward to have a better understanding of how to improve patient outcomes. Participants will debate the hottest topics in the field, in a variety of interactive and informative sessions.

The scientific programme will welcome an impressive list of experts who will speak about new perspectives and challenges in the management of COPD, severe asthma, IPF, asthma in children as well as debating different treatment alternatives and strategies.

The meeting also provides an excellent opportunity for networking in person with some of the world's leading experts in the respiratory field and to re-connect after such a long period of only online meetings.

The REG Summit 2022 will be the year's most important meeting in the field of respiratory real-life research, and everyone is encouraged to participate and get involved with the REG and its projects.

We look forward to seeing you safely in Barcelona!

WHAT REG MEANS TO ME

What Respiratory Effectiveness Group (REG) means for me?. In 2016, during the European Respiratory Society Annual meeting in London, I was invited to attend a meeting of "a pulmonary research group". I was told that this group had a different approach in doing clinical investigation, and were interested in doing research on "real world patients". The concept was very intriguing to me. After being an investigator in multiple pharmaceutical company-sponsored COPD clinical trials; and participated in NHLBI observational cohorts; I was always concerned about the difficulty in applying the studies' results to my patients. Clinical trials and cohort programs involved a "selected' patient population" due to multiple inclusion and exclusion criteria that were needed to enroll a homogenous patient population. I remember that the meeting took place at the historic London Medical Society Building. I thought, what a great place to get to know a group of investigators with a different approach to clinical research. I was fascinated by the dynamic interaction of the participants and "friendly" international environment. I met clinicians from both primary care and pulmonary medicine, basic scientists, and undergraduate students from all over the world that were together for a common cause. At the beginning, I didn't understand the REG structure; how projects were developed; how was the research conducted; data collection; publications; funding etc. I learned that "working groups" were the core of the organization. I joined the COPD working group; learned their current projects and research opportunities. Several months later, I was invited to join the executive committee. Soon after, the REG organization underwent significant transformation. We were confronted with many issues at the same time, from lack of funding to the need to re-structure the organization leadership. It was clear to me that the future of REG was in jeopardy, and we may not be able to continue to support the working groups. It took a tremendous amount of work from the executive committee, working groups leaders and close communication with the sponsors to solve the challenges that the organization its not his confronting. REG today stands on very solid ground; his working groups are very active and continue identify new areas that need to be studied using real world clinical research. The pandemic instead of decreasing the REG working groups collaboration did the contrary and resulted in record numbers of publications. Going back to the initial question, What REG means for me? REG means to me, that when you get together people that are willing to work hard, collaborate and communicate an idea or clinical problem can be developed and resolved. REG has demonstrated that working together towards a common goal is possible; and at the end of the day, the objective is to have a significant contribution in our patients daily life. I am proud to be part of REG and I am looking forward to inviting many young investigators to keep this organization moving forward.

ANTONIO ANZUETO
Professor of Medicine, University of Texas Health, San Antonio, Texas, USA

I am the director of Respiratory Evaluation Sciences Program (http://resp.core.ubc.ca), a health outcomes research program that is dedicated to respiratory diseases. As a health outcomes researcher, I am concerned about the impact of respiratory-related interventions on the health of individuals and the public. Clinical trials generate critical 'efficacy' evidence on such interventions. However, the efficacy-effectiveness spectrum in respiratory medicine is particularly wide, and we have had several examples of treatments that showed promise in clinical trials but did not deliver in the 'real-world'. REG is the only international initiative with such a dedicated focus on how respiratory treatment works outside of the confine of clinical trials and in the community. Because of its unique focus, REG is the professional association of choice for me. It provides a unique opportunity to get connected to colleagues with the same professional interests from across the world. Involvement in REG has helped me be aware of topical questions and available data sources, and participate in international studies that could not be done within any single country. Without REG, the landscape of respiratory outcomes research would be scattered and disconnected.

MOHSEN SADATSAFAVI MD, PHD
Associate Professor and Associate Director – Research, Collaboration for Outcomes Research and Evaluation The University of British Columbia Vancouver, Canada

Medical evidence of efficacy and effectiveness is the center of all best medical practice for all adult and pediatric diseases.
Randomized control trials evidence is the tip of the iceberg. What is happening in the real world, with patients having more than one disease, more than one medication, fully influenced by their environment and digital technology, adds an additional evidence level that needs to be considered and explored.
In respiratory medical affairs we acknowledge and leverage this knowledge and expertise. That is why we fully count on REG as a professional objective group, to demonstrate their expertise and increase awareness on the importance of RWE, patient acceptability, usability and compliance in respiratory diseases and beyond. We believe through that data, REG will demonstrate to the different decision bodies its value and will enhance and change the medical practice of healthcare providers to better manage their patient's needs.
I take the opportunity to acknowledge the effort of REG in the big PEARL delphi exercise, by building dedicated guidelines for pediatric asthma while taking into consideration real world evidence data. Novartis encourages and supports any activity that will help better treat adult and pediatric patients.

XAVIER JAUMONT (M.D.)
Global Medical Head Xolair
Novartis Pharma AG
Basel, Switzerland

Since 2018 I am a proud member of the REG Technology working group. My involvement in respiratory research started in 2012 when I commenced my PhD. My thesis was about development of personalized medicine in primary care asthma and COPD patients. Technology played an important role in my projects and my background in psychology and epidemiology were an excellent combination for this topic. I have talked with patients and healthcare providers about the implementation of eHealth in respiratory care, developed a clinical decision model based on big data and evaluated an integrated care service for primary care asthma and COPD patients. After my PhD I worked as postdoc on eHealth at the primary care department of the University Medical Center Groningen and combined this position with a job as project manager eHealth in a primary care laboratory. After that, I got an appointment as assistant professor at the faculty of economics and business where I have learned relevant skills regarding implementation of technology and change management. Since the beginning of the COVID-19 crisis, I have been working for the Dutch ministry of health on the Covid applications, and I have advised the European Center of Disease Control regarding the evaluation of contact tracing applications: a very exciting and relevant topic! This summer a made a transfer to the University Medical Center Groningen as figurehead and assistant professor eHealth where I will work on research, education, policy and network regarding health and technology. As an REG member I can work with experts in my field from all over the word. This can lead to interesting collaborations and eventually to improved care for respiratory patients. Please contact me if you have any questions. More about me: https://www.rug.nl/news/2021/09/the-new-healthcare-from-ehealth-to-coronacheck

ESTHER METTING, PHD
Assistant professor, Epidemiologist B (SMBWO certified) and Psychologist University Medical Center Groningen Data Science Center in Health (DASH) University of Groningen Faculty of Economics and Business

OCTOBER 2021

WORKING GROUP UPDATE

ALLERGY WORKING GROUP

The group is currently discussing new project ideas in the areas of rhinitis and AIT.

TECHNOLOGY WORKING GROUP

A new study which aims to identify the acceptability and usability of a package containing a triple formulation digital inhaler, sensor, and app in patients with poorly controlled asthma has been submitted for funding and is being finalised. A research protocol is currently being written. Other potential areas of research are being explored in the next working group meeting.

COUGH WORKING GROUP

The group is discussing the next phase of the 'burden of chronic cough on adults in primary care in the UK' project.

ENVIRONMENT, EPIDEMIOLOGY & AIRWAYS WORKING GROUP

The collaboratively funded (AstraZeneca, Boehringer Ingelheim, Chiesi and Kindeva) inhaler choice & environment (ICE) project, which assesses the impact of inhaler choice on patient care and the environment, is under way. Two questionnaires were approved by the steering committee to measure asthma/COPD patient and HCP perspectives and experience. These questionnaires have been rolled out internationally, with many responses being received from around the world. A new section of our website outlines the study plan: https://www.regresearchnetwork.org/research-2/inhaler-choice-the-environment/.

ILD WORKING GROUP

A new steering committee has been formed to guide the development of a new project characterising ILD diagnosis through distanced electronic multidisciplinary team meetings (eMDTs) in the post-COVID era. This project will be a follow up from the group's previous paper 'The characterisation of interstitial lung disease multidisciplinary team meetings: a global study'. The project has several aims: to identify the optimal structure of an eMDT in the post-COVID era; to identify the optimal or standardised approach that can be developed for the digital environment; to identify limitations and resources needed for eMDTs; to produce a series of recommendations as to how best to optimise the pathway to ILD diagnosis in real-world practice via distance meetings; to capture opinion and challenges with post-COVID fibrosis and COVID-associated complications in the standardised approach for diagnosis. Funders have been approached.

COST EFFECTIVENESS WORKING GROUP

A proposal has been developed by the group for a project which aims to provide a global scoping review highlighting gaps in clinical COPD guidelines where cost of treatment is (not) considered, and to identify COPD specialist opinion and priorities of cost-effectiveness in development and practical implementation of guidelines. This project is currently seeking funding.

ADHERENCE WORKING GROUP

Work is progressing on a scoping review that will assess how the monitoring and management of adherence can be addressed with personalised medicine, including strategies that have been adopted to encourage adherence; the articles for inclusion are being finalised and an outline for the article developed. This will be followed by a second review that will assess how adherence is included within current respiratory guidelines.

In a Working Group meeting in April the group discussed potential projects to investigate whether adherence to asthma medication is protective for severe COVID-19 and whether those with certain asthma phenotypes are at greater risk from covid-19. The group also discussed the possibility of identifying general practices where patients with asthma generally have higher adherence to preventer medication with the aim of investigating what factors may contribute to their patient's greater adherence.

CHILD HEALTH WORKING GROUP

The PaEdiatric Asthma in Real Life (PeARL) project aims to produce evidence-based recommendations regarding controversial aspects of paediatric asthma is progressing. Following the publication of the results of a survey on research priorities in paediatric asthma in JACI In Practice the group is now working on three systematic reviews. One review on stable asthma management is currently in the writing phase and research is ongoing on the second investigating treatment for acute asthma exacerbations. A survey has been sent to healthcare professionals and other stakeholders to gather information on how paediatric asthma is currently monitored worldwide.

A database study is now getting underway that will assess the factors associated with a successful step down of Inhaled Corticosteroids (ICS) in both children and adults with asthma. A proposal has been developed for a project to determine the prevalence of severe asthma in children in UK primary care, and funding is being sought. This study will also determine which patients with potentially severe asthma are being referred for specialist assessment and which are being missed and are remaining treated solely in primary care.

COPD WORKING GROUP

A prospective, observational multicentre study is underway to assess the prevalence of suboptimal peak inspiratory flow in patients with COPD and assess the predictive value of peak inspiratory flow for COPD exacerbations and symptom burden. The study aims to recruit 400 patients. COVID-19 has unfortunately caused delays at many centres, however patient recruitment has now begun at 7 centres, and to date 155 patients have been recruited. The Working Group are currently developing a project for a risk prediction model that could be used at the time of COPD diagnosis to predict the 5 yr risk of having a severe exacerbation, in order to allow those at greatest risk to be given earlier, more intensive interventions. There have also been discussions around a future study to investigate macrolide use in those with COPD.

SEVERE ASTHMA AND BIOMARKERS WORKING GROUP

The Working Group are currently developing ideas around a potential project to investigate the predictive value of biomarkers in determining the response to biologics, along with associated comorbidities. There are also plans for a possible project to map the patient the journey to biologic treatment.

DATABASES AND CODING WORKING GROUP

Katia Verhamme has stepped down as the Working Group Chair and Jenni Quint will be taking on the role. The Working Group are working on publishing the results of the TORPEDO study- Towards Optimum Reporting of Pulmonary Effectiveness Databases and Outcomes: identifying a core dataset for asthma and COPD studies, and on developing future project ideas.

WHAT IS THE ADEPT COMMITTEE?

The ADEPT (Anonymised Data Ethics & Protocol Transparency) Committee is an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG) to govern the standard of research conducted on internationally renowned databases. The ADEPT committee comprises scientists with statistical and epidemiological experience, members with specific database related expertise, independent clinical experts.

The ADEPT committee have been commissioned to govern research conducted on databases across the world (as well as other pragmatic research) including:

- Optimum Patient Care Research Database (OPCRD)
- Implementing Helping Asthma in Real Patients Database (iHARP)
- International Severe Asthma Registry (ISAR)

The ADEPT review process involves evaluation of protocols in terms of their fulfilment of the following key criteria:

- Practice and patient confidentiality will be maintained
- The means by which confidentiality is maintained is clearly described
- There is a well-defined hypothesis or clear question to be addressed
- The database proposed are suitable for the research
- The methodology is considered appropriate and ensures patient confidentiality at all times
- There is scientific and academic rigor
- There are no sections of the protocol which would necessitate formal ethics approval where none has been sought
- The team are experienced in real-life research or are supported by experts with relevant real-life expertise methodologies.

Individuals or research groups interested in conducting a study using data from one of the listed databases must submit an application to the ADEPT committee for approval before commencing a research project. In addition, individuals or research groups interested in conducting a study using data from a database may approach the ADEPT committee for advice on methodology and standard of research to be conducted.

For more information including committee members, the ADEPT process and the application form can be found on the REG website: https://www.regresearchnetwork.org/adept-committee/

If you are interested to join the committee and volunteer as an application reviewer, please contact us at application@adeptcommittee.com

REG RESEARCH PROJECTS IN FOCUS

Peak Inspiratory Flow as a Predictor for COPD Exacerbations Project

Assessing the Utility of Peak Inspiratory Flow as a Predictor for COPD Exacerbations

This is an international, multi-centre, non-interventional study that aims to

- **Determine the prevalence of suboptimal peak inspiratory flow (PIF) and inadequate inhalers and the baseline characteristics of these groups**
- **Assess the role of PIF and inhaler choice in predicting COPD exacerbations and symptom burden.**
- **Assess the role of blood biomarkers and Th2 markers in predicting COPD exacerbations and the variability and correlation of PIF with other biomarkers and lung function measurements in stable COPD.**

Rationale

Dry Powder Inhalers (DPIs) require that patients have sufficient peak inspiratory flows (PIF) to disaggregate the powder into particles that can adequately be inhaled into the lower respiratory tract1.

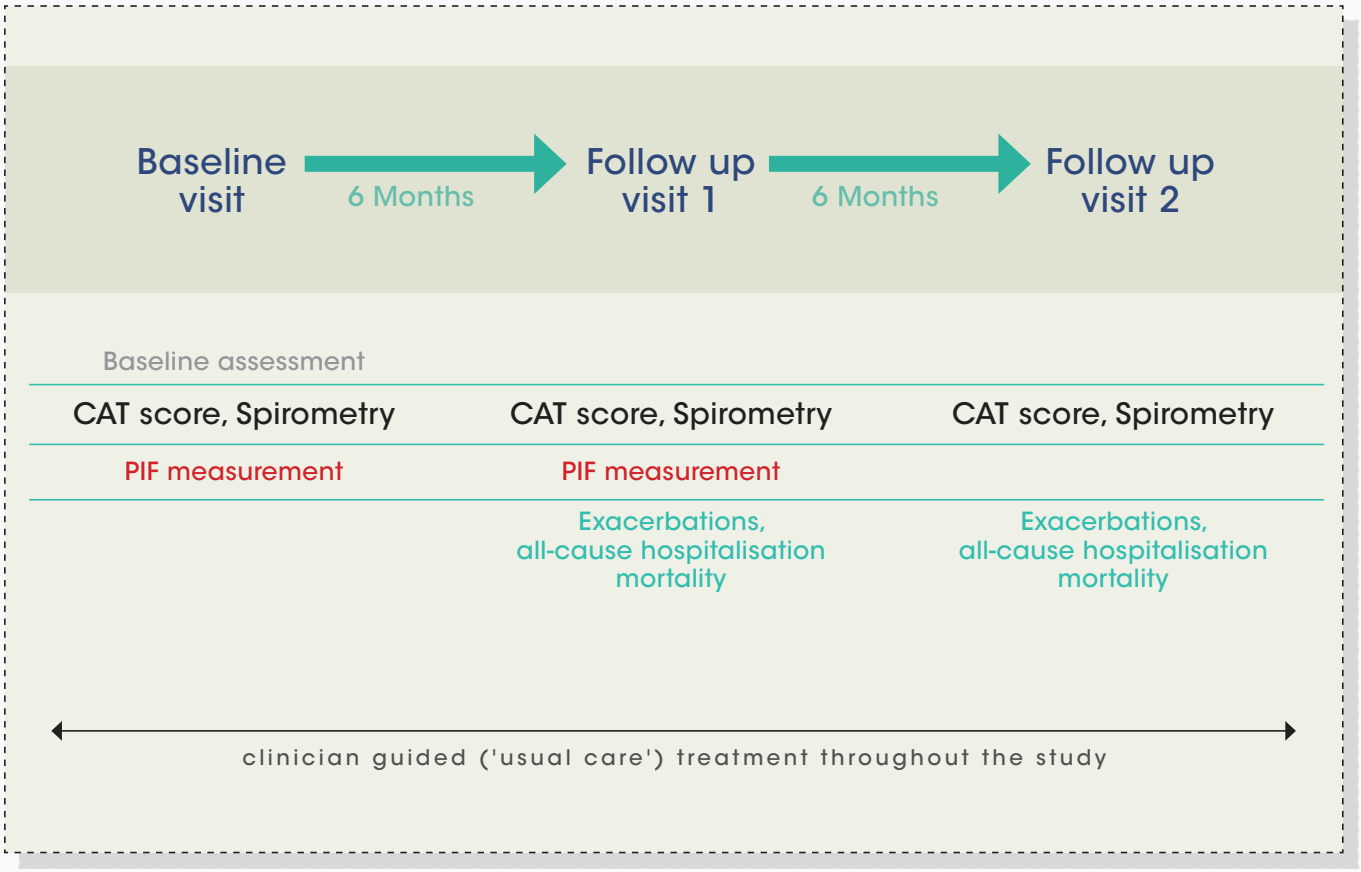
The prevalence of suboptimal PIF in studies has varied greatly between studies and there is mixed evidence from previous studies as to whether PIF correlates with other measures of lung function.

Following hospitalisation for a COPD exacerbation suboptimal PIF has been associated with a higher risk of readmission for COPD and worse symptom burdens4.

There is a need to further assess PIF particularly in stable COPD patients and in a larger, multi-centre study to investigate the predictive value of PIF in terms symptom burden and future exacerbation risk.

Study design

This is a 12 month prospective observational study,
with a baseline visit and 2 follow-up visits at 6 and 12 months.



Study Steering Committee

Omar Usmani (Chief Investigator) / Marc Miravitlles / Sinthia Bosnic-Anticevich

Status

This study is looking to recruit further centres (primary or secondary care). If you are interested in participating as a centre and would like further information please contact Sarah (sarah@regresearchnetwork.org).

This project is supported by Boehringer Ingelheim.

Inhaler choice & the environment

The impact of inhaler choice on climate change and personalised healthcare

The Environement, Epidemiology and Airways Working Group is conducting a research project looking at Inhaler Choice and the Environment (ICE).

Objective of ICE

This research will provide expert opinion and consensus of physicians and health care workers on:

- **Costs to environment: The impact of inhaler choice and switching inhaler delivery system on climate change, as well as short-term vs long-term solutions for reduction of impact.**

The research will also gather information from patients on:

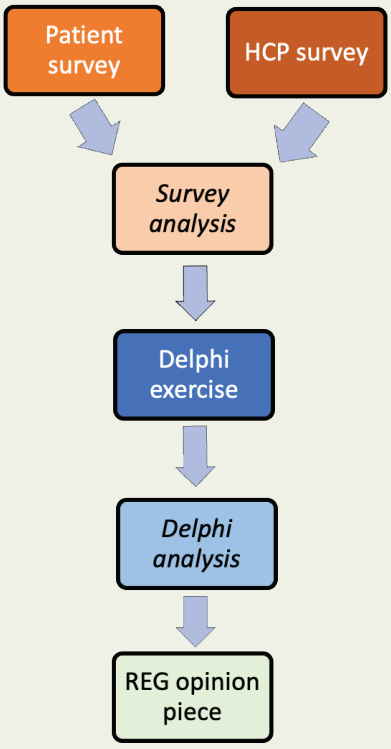
- **Personal impact: The impact of inhaler choice / changing medication that has affected their personalized healthcare plan and inhaler use.**

Rationale

Medications for asthma and COPD are mostly administered using inhaler devices. Inhalers are crucial to managing daily symptoms, acute emergencies and chronic disease. Most of the current inhaler devices available provide therapy using one of three drug delivery systems: dry powder inhalers (DPI), metered-dose inhalers (MDIs +/- spacers/holding chambers, and breath-actuated MDIs) and soft mist inhalers (SMIs).The potential benefits and drawbacks of inhaler delivery systems and their impact on patient care is well documented, but there has been limited discussion on the contribution of inhaler choice to climate change and personalised healthcare.This research aims to gather patient-centric expert opinion to deliver consensus on the impact of switching inhaler type on climate change and the suggestion of green alternatives to switching inhaler types; as well as measure the impact of switching on patients and their personalised healthcare plan. Extra focus will be given to switching inhaler type for non-medical reasons (i.e. based on policy change, rather than patient health requirements); and offer perspective on driving inhaler development for carbon reduction. It will also provide an update of the current discussion in the literature on the impact of inhaler choice to provide support to the consensus.

Methodology and Outputs

The study will be carried out in 3 parts leading to 3 outputs:



Part A: International data collection using two questionnaires

- Surveys designed using literature
- Survey 1: Distributed to asthma / COPD patients
- Survey 2: Distributed to healthcare professionals working with asthma / COPD patients

Part B: Delphi exercise

- Questions defined by results form Part A
- 15 to 30 participants
- Prioritised by contribution/expertise
- 2 rounds

Part C: REG opinion piece

- REG participants shown results from Part A/Part B
- Consensus/define research priorities/recommendations

Part A: International data collection using two questionaires

The aim of the questionnaires is to identify key needs, opinions, priorities and values in inhaler choice and the potential impact of switching delivery systems on patient care. Patients and healthcare professionals will also be asked about greener alternatives and whether they are or will be used in practice. The scope of questions for the survey will be to gauge opinion on:

1. **Characteristics** – To gather general information on patient (such as demographics, diagnosis, inhaler switch and inhaler brand) and HCP (such as their region of work).
2. **Personalised healthcare / inhaler choice** – To identify satisfaction, opinion and considerations of patients and HCPs on their choices in inhalers/healthcare plan
3. **Inhaler satisfaction** – To ascertain patient confidence and satisfaction with their (new) inhaler

4. **Climate change** – To gain insight into awareness and attitudes towards inhaler impact on climate change, green inhaler alternatives and green alternatives to switching inhaler (such as recycling).

These results will inform the survey design for the Delphi exercies (see below). The results of part A will be analysed and compared to the literature, leading to the development of a manuscript for submission to a peer-reviewed journal.

Part B: Delphi exercise

A modified Delphi survey will be designed based on the results from the patient/HCP questionnaires and sent to participants to identify and prioritise key issues in inhaler choice in personalised health care, changing delivery systems and development of green alternatives. Focus will be directed to raising key themes and questions of the impact of inhaler choice on climate change and patient care. The second round of the Delphi exercise will aim to reach consensus on the needs identified in phase I Delphi and evidence provided by the survey responses. Evidence from the Delphi surveys will be reviewed and interpreted, and priorities among the groups will be compared, identifying common priorities and commenting on any discrepancies.

The results from the Delphi will be analysed and compared with the literature, and a paper for submission to a peer-reviewed journal will be developed.

Part C: REG opinion piece

The final output of this study will be a structured expert consensus/opinion piece which offers a clear concise statement on the impact of inhaler choice/switch and policy on both the environment and patient care and potential alternative solutions to balancing the needs of the patient and the needs to reduce environmental cost in short- and mid-term vs long-term. The consensus will include recommendations for quality improvement driving carbon reduction and development of low carbon propellants to avoid policy-based inhaler switch as opposed to patient needs. To be submitted for publication in peer-reviewed journal.

Study Steering Committee

Omar Usmani (Chief Investigator) / Sinthia Bosnic-Anticevich / Nicolas Roche

Status

Part A of this study is in active recruitment for patients and HCPs. If you are interested in participating in the survey or would like to pass on to colleagues or patients, please visit https://www.regresearchnetwork.org/research-2/inhaler-choice-the-environment/

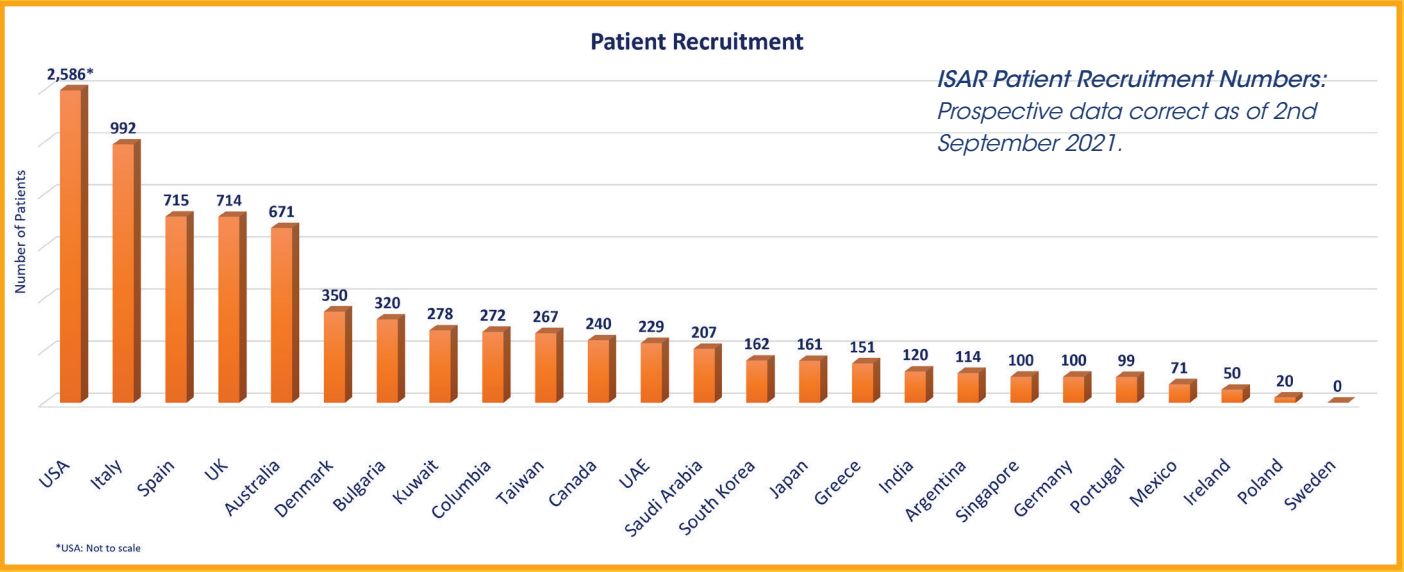
If you would like further information, please contact Graham (graham@regresearchnetwork.org).

This project is suported by AstraZeneca, Boehringer Ingelheim, Chiesi, Kindiva

INTERNATIONAL SEVERE ASTHMA REGISTRY

ISAR So Far

The International Severe Asthma Registry (ISAR) marches on into its 4th year with data from 11,555 severe asthma patients (including 8,889 patients with prospective data) from our 23 collaborating countries. ISAR is delighted to announce and welcome Poland as our newest collaborator to the registry. Our plan is to continue growing and welcome France and Brazil later this year. Additionally, we are delighted to announce an 18-month extension for ISAR funding till November 2023!



ISAR Publications in 2021

With 3 studies accepted and published in 2021 (see table below for more details) and 8 more submissions planned for 2021, ISAR continues to contribute to the development of high-quality academic research that will build on our understanding of severe asthma management and care. We are also pleased to share our involvement in an academic publication regarding severe asthma super-responders published in The Journal of Allergy and Clinical Immunology: In Practice.

Kerkhof M, et al. **"Asthma Phenotyping in Primary Care: Applying the International Severe Asthma Registry Eosinophil Phenotype Algorithm across All Asthma Severities"** *J Allergy Clin Immunol Pract,* 2021

The ISAR eosinophil phenotype gradient algorithm, when re-applied in a UK primary care cohort, found that eosinophilic asthma predominates in primary care and is associated with greater asthma severity and healthcare resource utilisation. This algorithm enables primary care physicians to identify and categorise patients into those with and without eosinophilic asthma and refer them, when appropriate, for phenotype-targeted treatment. Click **here** to read the full article!

ISAR Publications in 2021

Heaney LG, et al. **"Eosinophilic and Noneosinophilic Asthma: An Expert Consensus to Characterize Phenotypes in a Global Real-life Severe Asthma Cohort"** *Chest,* 2021

We characterised severe asthma patients according to discrete phenotypes through the development of a multicomponent, consensus-driven, and evidence-based eosinophil gradient algorithm, and found that the eosinophilic phenotype was more prevalent than previously thought. Click **here** to read the full article, and **here** for the publication slide deck.

Denton E, et al. **"Cluster Analysis of Inflammatory Biomarker Expression in the International Severe Asthma Registry"** *J Allergy Clin Immunol Pract,* 2021

Through a hierarchical cluster analysis of biomarkers, we found that a high degree of biomarker overlap drove the development of 5 distinct patient clusters, each associated with unique patient characteristics. These results pave the way for future research to characterise further stratified severe asthma phenotypes and better measure treatment response. Click **here** to read the full article, and **here** for the slide deck.

Upham J, et al. **"Defining a Severe Asthma Super-Responder: Findings from a Delphi Process"** *J Allergy Clin Immunol Pract,* 2021

A consensus definition of a severe asthma super responder was defined using a modified Delphi process. This is a vital prerequisite for better understanding super-responder prevalence, predictive factors, and the mechanisms involved. Click **here** to read the full article!

ISAR Steering Committee Meeting: 11th May 2021

A **The meeting was a success with 29 international ISC members, representing over 19 international countries in attendance**

B **ISAR were able to provide the ISC with updates on the latest ISAR initiatives and developments including:**

- Optional CoVID-19 bolt-on questionnaire (17 patients from 4 countries with a positive history of CoVID-19 infection to-date)
- Upcoming site & country-level asthma care reports providing an overview of longitudinal patient data trends

2021 Research Proposals

Following the annual research prioritisation exercise held during the ISAR Steering Committee (ISC) meeting earlier this year, we are delighted to confirm the two new fully funded research projects which have been prioritised by the ISC.

1. Phenotypic characteristics, comorbidities and response to therapeutic interventions associated with non-type 2 asthma (EMBER)
2. Effectiveness of biologics (by classes) in patients with different combination of T2 biomarkers (IGNITE) ISAR also received 7 network proposals (non-funded academic studies). Meetings are being scheduled to kick off these initiatives!

ENLIGHTEN: ISAR Research (18 Projects)

What Severe Asthma Looks Like:

1. Characterisation of severe asthma worldwide: data from the International Severe Asthma Registry (11/*2019*)
2. The role of exacerbations on lung function trajectory
3. Characteristics of the eosinophilic asthma phenotype (04/2021)
4. Biomarker relatability in ISAR ***(BRISAR)*** (02/*2021*)
5. Patterns of onset & associated phenotypes ***(PATH)***
6. Phenotypic Characteristics and response to therapeutic interventions/ Characteristics and comorbidities associated with non-type 2 asthma **(EMBER)**
7. *What is the prevalence of alpha-1 antitrypsin genetic abnormalities in severe asthma and do the characteristics of patients with such abnormalities differ from those of severe asthma patients without such abnormalities?*

Appropriate Care for Severe Asthma:

1. Hidden severe asthma in primary care (12/*2020*)
2. Real world biologic use and switch patterns in severe asthma **(SUNNIE)**
3. Global access to severe asthma biologics **(BACS)**
4. Differences in asthma disease severity by socioeconomic status and ethnicity **(RADIANT)**
5. Descriptive Study of the Incidence of Malignancy in Severe Asthma Patients Receiving Benralizumab and Other Therapies, a Post Authorization Safety Study **(PASS)**
6. Is there a trough phenomenon with worsening asthma in the last week of a dosing interval for q monthly and bimonthly biologics? If present, which patient characteristics are associated with the phenomenon, and can it be shown objectively?
7. Should pulmonary function (the degree of bronchial obstruction) be considered a necessary component of "complete response" definition and, in consequence, should it be considered an independent therapeutic objective?
8. ConectAR - Collaborative research network: Advancing patient and public involvement in Respiratory and digital health
9. To evaluate inter-observer agreement in the choice of biologic therapy for severe asthma patients among severe asthma specialists, based on assessment of real-life clinical cases
10. Leveraging microbiome analysis in the assessment and management in patients with severe asthma
11. Microbiome-guided use of biologics in severe asthma patients

Effectiveness of Biologics:

1. Comparative effectiveness across severe asthma biologic classes (anti-IL5 vs anti-IgE) in patients eligible for both ***(FIRE)***
2. Define responders and non-responders to biologics ***(BEAM)***
3. Impact of initiating biologics in patients on long-term OCS or frequent rescue steroids ***(GLITTER)***
4. Biologic patterns, clinical outcomes and health resource utilisation ***(CLEAR)***
5. Describe clinical outcome before & after biologic treatment ***(LUMINANT)***
6. Impact of comorbidity on response to biologics in severe asthma ***(PRISM)***
7. What is the effectiveness of biologics (by classes) in patients with different combination of T2 biomarkers **(IGNITE)**

If you wish to submit a research question utilising ISAR data, you may do so via the **"submit a proposal or research request"** tab on ISAR website.

ISAR Website

The ISAR website has had a facelift. It now contains a new "Dissemination" tab for the latest news on ISAR abstracts and publications, and a "FAQ" tab which provides answers to frequently asked questions about ISAR.

www.isaregistries.org

ACKNOWLEDGEMENTS

The work of REG would not be possible without the contributions from our invaluable supporters to fund innovative research projects developed by our expert Collaborators.

REG is looking to launch a number of ambitious research initiatives which offer the opportunity to impact clinical management guidelines and patient care.

We welcome any suggestions from Supporters and would be happy to discuss your ideas in more detail.

You can always get in contact with the REG team by email at
enquiries@regresearchnetwork.org,

or write to Michael Walker, REG CEO at
michael@regresearchnetwork.org

GOLD SUPPORTERS

AstraZeneca

NOVARTIS

SILVER SUPPORTER

Boehringer Ingelheim

Theravance

We would also acknowledge the support of the following companies:

opc UK

Roche

SANOFI GENZYME

teva

Chiesi
People and ideas for innovation in healthcare

Kindeva
DRUG DELIVERY