# ADVANCES IN... REAL-LIFE RESPIRATORY MEDICINE

The Respiratory Effectiveness Group Newsletter

### Prioritizing REG Research in 2015

All the activities we undertake – setting standards, publishing reviews and position statements, hosting summits and applying for sessions at wider society events - are integrally linked with our research efforts. Some help to provide a framework for research while others help to strengthen the impact and value of our data by raising the profile of the field and by seeking to reach new audiences so that valuable real-life evidence can help guide clinical practice.

#### Year 1 research (2013)

REG kicked off a number of academic studies to address unmet research needs identified at our first Council ("Arch") meeting; develop working relationships within the REG network and generate the reputation for high-quality standards and data (the "collateral") we needed to advocate for a change in the way the field is viewed

#### Year 2 research (2014)

REG implemented a transparent research funding approach and reached out to the expertise in (and beyond) the REG network to identify the pressing questions in the respiratory field that real-life research could help to address. The research call led to a "Research Pin Board" where academic research ideas could be submitted and curated. The ideas were prioritized by our Research Review Committee (in terms of their quality of design, clinical relevance, feasibility and alignment with REG's core objectives). The top two studies were awarded REG Core research grants

in April (one is underway; the other in protocol development) and two further ideas within the top ten were supported by provision of data for analysis.

#### Year 3 research (2015)

Our original steering groups have matured into working groups and have been supplemented by a very well established group (in the Small Airways) as well as a number of newly-formed working groups. Each working group is targeted at an area of respiratory medicine for which real-life research methods offer particular value. With so many ideas being generated by our working groups, we do not intend to send out a separate call for research this year. Instead, on October 31st, all ideas that are currently passing through the working groups will be collated and submitted to the Research Review Committee for prioritization.

The process will generate a list of prioritized research needs, endorsed by the organization that can be targeted to (or by) external funders, but also provide us with a list of studies that REG (as a not-for-profit) can support through reinvestment of available funds at financial year end, i.e. through our core grant funding stream.

Spontaneous research ideas are still welcomed throughout the year.

These should be submitted to Alison Chisholm (alison@effectivenessevaluation. org) who will help direct the idea to a relevant working group where she can work with you, and with the support of the working group, to develop the concept further.

#### SECURING FUNDING RESEARCH IDEA 31 October 2015 GENERATION If insufficient REG Funds, continue to look externally REG develops idea in collaboration with WG OR seeks dedicated Working Groups research grant Identify Research lature of funding dictates future study course: Single commercial funding source: an investigatinitiated study conducted external to REG Non-productbrand specific grant(s): an REG Collaboration carried by REG or in partnership respective fields of expertise

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Early information on next year's REG Summit and details of how you can get involved in shaping the agenda...

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#### **Working Group Updates**

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#### Optimum Patient Care Research Database

Find out more about this fantastic resource, open to all REG Collaborators, and how you can submit a request to make use of the database in your research.

turn to p6 for more information

### 2016 REG ANNUAL SUMMIT

### Working in partnership with ASTRO-LAB

We can confirm that the 2016 REG Annual Summit will take place on the 15-16th of April 2016 in Lyon, France to coincide with final results symposium of ASTRO-LAB (Assessment of the safety of Long-acting Beta Agonists in Asthma Routine Care by combining healthcare databases and direct patient follow up).

ASTRO-LAB is funded by the European Commission (EC) through the Seventh Framework Program (FP7). The aim of the project is to provide new information about the benefit/risk ratio of LABAs for asthma management. It addresses several important knowledge gaps by focusing on both adults and young people with asthma, and

on the benefit/risk ratio of LABAs taken with ICS.

The ASTRO-LAB investigators are also examining:

- · How people with asthma use LABAs and ICS inhalers;
- · What influences their decisions on how they use inhalers;
- · The care they receive from their clinicians, and
- · What determines how their clinicians help them manage their asthma.

The ASTRO-LAB findings will be used to formulate recommendations on the use of LABAs and ICS for the treatment of asthma, and ways to improve the support offered to adults and young people with asthma in primary care.

We are delighted to be working with ASTRO-LAB on our summit: the partnership allows us to welcome ASTRO-LAB stakeholders (including EU funders, regulators, respiratory clinicians and allied health professionals) to take part in REG events and also opens up the opportunity for current REG collaborators and supporters attend the ASTRO-LAB events and speak with ASTRO-LAB delegates.







#### **Volunteers Needed for REG 2016 Annual Summit Committee**



We are currently looking for volunteers from within the REG network to form a committee for the REG Annual Summit. Participating in the committee will allow you to contribute your ideas to develop the theme of the two-day event and shape the agenda to ensure that we deliver valuable sessions which represent the diversity and expertise of the group.

If you would like to join the REG 2016 Summit Committee or if you have any suggestions for themes, guest speakers or topics you would like to be added to the agenda, please contact Zoe Mitchell: zoe@effectivenessevaluation.org

### Thank You...

#### **Gene Colice**

We are very sad to announce that one of the REG's original and most active collaborators - Gene Colice - is stepping down from his roles as:

- · Adherence Working Group Lead;
- · Member of the Small Airways **Study Group.**

Gene has been a generous and valued member of the SASG since it was first formed in 2008.

During his tenure with the SASG and REG, Gene has helped to deliver extensive research publications and has been an active and valuable collaborator across the REG network.

Gene will remain as co-author on all SASG study manuscripts that he has contributed to. We look forward to continuing to work with him in the future as a REG Supporting Collaborator.

#### **REG Experts Reaching Out Across The World**

We are grateful to the many REG collaborators who have presented and chaired a range of well-received sessions, symposia, abstracts and posters at a range of international congresses. To date this year REG has been represented with seven different activities across the APSR, World Asthma Allergy Forum, IPCRG 2015, ATS 2015 and EAACI 2015. Our thanks to the speakers, moderators and researchers who have helped us raise the profile of real-life research this year:

Daryl Freeman, David Price, Dermot Ryan, Helen Reddel, Jerry Krishnan, Mike Thomas, Nicolas Roche, Omar Usmani, Osman Yusuf, Peter Smith, Richard Lockey, Rupert Jones, Santiago Quirce, Tan Tze Lee, Todor Popov, Vibecke Backer and Victoria Carter.

We are looking forward to many further presentations at conferences across the globe for the rest of 2015 and are already planning a comprehensive programme for 2016.

#### **Our Supporters:**

















Aerocrine

13<sup>th</sup>:

### **Events**

### 2015 REG Events Calendar

As announced in our Spring newsletter, we are taking a strategic approach to future event attendance – seeking to maximise our representation at key events around the world with the resources available to us. A list of up-coming events (for 2015) are summarised to the right, illustrating the geographical spread of our activities – London, Amsterdam, Milan, Seoul, Prague.

We are indebted to the number of REG Collaborators who present at conferences across the world (p2) and to everyone who takes time out of their busy schedules to attend the many working group, project and committee meetings held to dovetail with the events. We are also greatly impressed by the increasing number of session proposals being submitted spontaneously on behalf of REG by our collaborators.

We have already submitted for consideration of inclusion in the scientific programmes of a number of global conferences in 2016 – in the USA, South America, Asia Pacific and Europe. We'll share the details as soon as we receive confirmation of acceptance involved.



#### **SEPTEMBER:**

#### ERS 2015, Amsterdam:

25<sup>th</sup>: Working Group Meetings

**REG Council meeting** 

26<sup>th</sup>: REG AGM Working Group Meetings

#### **OCTOBER:**

17<sup>th</sup>:

#### WAO World Allergy Congress, Seoul

REG Symposium: Harnessing the Real World to Address Unmet Needs in Allergy Care

#### **NOVEMBER:**

#### ISPOR 2015, Milan, Italy

10th: Panel Session - Best available evidence for HTA decisionmaking: Efficacy or Effectiveness?

#### **NOVEMBER:**

#### ESPACOMP 2015,

#### Prague, Czech Republic

Measurement of inhaled costicosteroid adherence using electronic healthcare data: impact of methods on MPRs

#### **DECEMBER:**

TBC:

### British Thoracic Society Conference, London

TBC: The cost of steroid induced morbidity among severe asthma patients in

the UK

Evidence of prescribing errors in primary asthma care

### REG events at the 2015 ERS Conference

#### September 25<sup>th</sup> (Wyndham Apollo Hotel, Amsterdam)

08.00–09.00 Patient-Centred Outcomes Research Institute (PCORI) Grant Planning

09.00-10.30 ACOS Working Group Meeting

11.00–12.30 Allergy Working Group Meeting

12.30–14.00 Databases, Coding & Validation Working Group Meeting

14.00–15.30 IPF / ILD Working Group Meeting

15.30-17.00 COPD Control Working Group Meeting

17.00–18.30 Small Airways Study Group (SASG) Meeting

19.00-... Council Dinner \*\*Closed Door Meeting\*\*

### September 26<sup>th</sup> (Wyndham Apollo Hotel, Amsterdam)

08.00-09.30 Annual General Meeting

09.30-11.00 REG / EAACI Taskforce Meeting \*\*Closed Door Meeting\*\*

11.00–13.00 Technologies Working Group Meeting

13.00–14.30 Adherence Working Group Meeting

15.30-17.00 Biomarkers Working Group Meeting

17.00–18.30 Child Health Working Group Meeting

19.00-20.00 Joint Committee Meetings \*\*Closed Door Meeting\*\*



### **WORKING GROUP UPDATES**

#### Biomarkers Working Group – Inaugural Meeting



June saw the first Biomarkers Working Group Meeting, bringing together international experts from a range of disciplines to discuss new research ideas. publications and future collaborations. The Group grew from the European FeNO Working Group (EFWG), an initiative supported by Aerocrine to review existing data and promote the concept of inflammometry in clinical practice.

Last year, the EFWG decided to move away from a single sponsor in order to deliver independent position statements and consider all biomarkers, rather than FeNO alone. The Group aims to:

- · Advocate for the use of inflammometry in daily practice;
- · Establish how inflammometry can

be used to better target therapies in real-world settings.

The initial discussion centred on the new National Institute for Care Excellence • Elevated FeNO and Blood Eosinophils (NICE) Guidance and its implications and how to increase the evidence for the role of FeNO in on-going management. The discussions were UK-centric because of the intended response to NICE and because of the free access to the UK Optimum Patient Care Research • Link between eosinopenia and Database as a research resource through

Although initial studies may use the UK data (OPCRD), the REG network can access other national databases around the world to repeat (and validate) studies and longer term, the Group aims to include representatives from a number of different countries who can provide insights into the means by which biologics can be accessed in their territory.

A number of research ideas were discussed using the OPCRD and other research databases to evaluate and consider:

- Utility of blood eosinophils as a predictor of outcomes
- Utility of blood eosinophils as a predictor of response to therapy - dual bronchodilation vs ICS/LABA
- Link between smoking and FeNO level
- Pulmonary vs systematic drivers of high blood eosinophils
- increased risk of pneumonia
- Opportunities to use biomarkers in the upper airway

Early publication plans include an editorial discussing the differences between NICE and GINA statements on FeNO with a focus on inflammometry and a review on the role of eosinophils / inflammometry in airways disease.

The next meeting will take place in Amsterdam on Friday 25th September 14.00 - 15.30.

#### Taxonomy of Adherence Expert Panel Meeting



REG convened an expert panel in Barcelona in June during the EAACI 2015 Conference in order to discuss the issue of medication adherence in asthma and COPD. As a result of the one-day panel, the team of experts has agreed to work together in the long-term as a Working Group within REG. The first project will be the development of the outputs from the panel meeting into a collection of papers for a journal special issue on

adherence in respiratory medicine and the taxonomy of adherence.

Studies consistently demonstrate suboptimal adherence to inhaled respiratory medications, but they also reveal substantial variation in results owing to use of different methods and terminology for assessing and referring to adherence. Standardization of taxonomy will assist in the identification of different types of adherence and support research as common approaches, definitions and outcomes are consistently applied across studies so that greater research efficiencies are realized.

The Group will consider the wide-ranging and complex issues affecting adherence to respiratory therapies on a macro-(system), meso- (physician / practice) and the microlevel of individual patients.

Some of the papers delivered will synthesise concepts shared during the panel and will include some previously unpublished data to illustrate the key discussion points. The collection of papers will also include original research, publishing for the first time the model of

adherence determinants developed by the EU FP7-funded project ASTRO-LAB. The planned papers will draw on a number of common features:

- Application of taxonomy
- The ASTRO-LAB model
- Identification of future research needs.

The next meeting will take place in Amsterdam on Saturday 26th **September from 13.00 – 14.30.** 

### **Newly Appointed** Adherence Working **Group Lead**

We are delighted to confirm that following the retirement of Gene Colice from the role, Eric Van Ganse from the University of Lyon will be taking on the role of Adherence Working Group Lead.

Eric has recently been leading the EU-funded ASTRO-LAB project, which looks at the safety of LABAs in asthma managment, and also closely at adherence to asthma medications.

### WORKING GROUP UPDATES

A quick roundup of activities taking place across the REG working groups...

#### **Technologies Working Group**

The Technologies Working Group is currently working on consolidating research ideas ahead of the first face-to-face meeting in Amsterdam in September. Additionally, a session proposal for the ATS 2016 is in progress and you may have already seen information on the work of PhD researcher Sam Howard, regarding his investigation into attitudes towards new Electronic Medical Devices for Asthma Treatment.

Links to the survey are available on the REG website and will be distributed via the new REG email newsletter - the Group appreciates your support in completing this survey. The Technologies Working Group is also supporting an examination of the concept that too many alarms are sounded in critical care medicine, to the point that they seldom illicit the action intended. Input is needed from clinicians (~15-min structured telephone/Skype interviews) to ensure the results are clinically meaningful, i.e. what are the drivers of alarm fatigue from a clinical perspective.

**Critical Care Input Required for Alarm Fatigue Study** 

If you work in critical care and/or ventilation settings and/or have a colleague who may be interested in getting involved, please contact Alison Chisholm (alison@effectivenessevaluation.org).

#### **ACOS Working Group**

The first project the ACOS Working Group is focussing on is a Proof of Concept study that will evaluate different definitions of ACOS within and across a range of international databases. The recently published GOLD/GINA definition of ACOS is considered a working definition/description rather than a gold standard and the ACOS Working Group believe there is a need to develop a set of standardized definitions for consistent use within future ACOS research. With a view to taking the KIS (Keep It Simple) approach, the study will identify different population definitions of ACOS and evaluate how well they agree within and between databases.

#### **COPD Control Working Group**

Having proposed the concept of control in COPD in a recent paper in the International Journal of COPD, Marc Miravittles and the COPD Control Working Group are now seeking to test its clinical validity and utility (i.e. in terms of predicting outcomes and guiding and tailoring COPD management). A series of validation projects are now underway, including a database pilot and a prospective, multicentre validation study involving an international cohort of routine care / unselected COPD patients. The prospective study planning will continue at the COPD Control Working Group Meeting at the ERS on Friday 25th September (3.30-5.00pm).

#### IPF / ILD Working Group

A study protocol has been developed examining missed diagnostic opportunities provisionally titled Identifying opportunities for earlier diagnosis of idiopathic pulmonary fibrosis in routine care in the UK: A retrospective clinical cohort study and funding avenues are currently being explored. A further study Evaluating Agreement and Accuracy Of Interstitial Lung Disease (ILD) Multi-Disciplinary Team (MDT) Diagnosis Across A Range Of Global Geographies and Healthcare Settings is currently in development.

#### **Small Airways Study Group**

We are delighted to have integrated this prolific group fully into the REG network. The Group currently have a number of manuscripts in preparation and a number of new studies proposals in development.

#### **REG Study News**

REG has witnessed an explosion of projects coming from the many productive Working Groups across the REG network of collaborators. As a result of our productive Working Groups, we have a number of abstracts to be presented at ERS 2015 in Amsterdam in September.

- Predictors of frequent severe asthma exacerbations (Asthma Risk Predictors Working Group)
- Characterisation of real-life, longitudinal ICS adherence patterns in a UK asthma population (Adherence Working Group)
- Predicting asthma exacerbations in children an observational study in real life (Child Health Working Group)
- Prescribed doses and effect on asthma treatment outcomes of extrafine (ciclesonide) vs standard particle inhaled corticosteroids (ICS) (Small Airways Study Group
- Dose-response effect of small particle vs standard particle ICS on severe asthma exacerbations by sex (Small Airways Study Group)

REcognise Asthma and Link to Symptoms and Experience (REALISE™) Asia is a recently completed survey-based study of asthma patients and physicians in Asia. In addition to subjective and objective levels of control among participants, the survey also characterized patients' attitudes towards their asthma. REG has initiated a REALISE Asia Delphi Study to identify targeted management recommendations for different attitudinal cohrots identified within the REALISE Asia population to help optimise clinical outcomes. The Delphi procedure is now complete and a manuscript is in development.

Other recent research highlights include:

- Commencing a study designed to explore optimal management options in pre-school asthma/wheeze, led by Dr Jonathan Grigg and supported by both the Small Airways and Child Health Working Groups.
- Provision of data for two database studies that will be carried out by the IPCRG's UNLOCK group.

### Taskforce: Asthma Comparative Effectiveness Research Quality Standards

The European Academy of Allergy and Clinical Immunology / Respiratory Effectiveness Group (EAACI/REG) Taskforce on Quality Standards in Asthma Comparative Effectiveness Research (CER) has been making significant progress since its inception.

The Taskforce was set up to conduct a systematic critical review and appraisal of the real-life study literature in asthma, published between 2009 and 2013. The resultant taskforce report will describe the current quality of real-life research in asthma; highlight studies worthy of possible integration into asthmarelated guidelines and policy decisions, and recommend quality targets for the future.

The taskforce outlined the following key steps to achieve its stated objective:

- Development of a quality checklist for scoring the real-life asthma literature, based on a review and synthesis of existing, published quality standards (e.g. extended CONSORT, STROBE, REG quality standards, etc.);
- Identification of real-life asthma studies published in peer review journals during the last five years (2009–13);
- Appraisal of the literature using the taskforce quality checklist;
- Identification (and characterization) of well-designed real-life studies that could be up-graded from (GRADE-defined) low-quality data and that may be worthy of consideration by future guideline developers;
- Explanation, where relevant, for apparently conflicting results between high-quality real-life studies and randomised controlled trials that (appear to) address the same/similar research question(s).

Once the taskforce was underway, a number of decisions were taken to ensure the operational feasibility of the taskforce's goals. The following refinements were required to the scope of the literature review:

- Real-life asthma literature was refined to include only comparative effectiveness observational asthma studies;
- Five year review period was extended to ten years.

The search was focused on four PICOT questions, targeted at gaps in the existing RCT evidence:

- Influence of adherence on asthma outcomes;
- Influence of device type on asthma outcomes;
- Influence of smoking history on asthma outcomes;
- Influence of inhaled corticosteroid (ICS) particle size on asthma outcomes.

For ease of use and access, it was agreed to use Excel for development of a QA tool which aims to:

- Operationalize existing recommendations / quality standards;
- Develop a user-friendly tool with minimal opportunity for misinterpretation and inter-rater variability;
- Develop a tool to enable the retrospective evaluation of published observational CER asthma studies;
- Include primary mandatory fields / quality criteria and secondary criteria that are "qualifiers" and further describe the strengths and weaknesses of the papers.

#### Phase la: Literature review

The literature review was led by taskforce lead, Nicolas Roche, with support from REG.

An initial broad search was narrowed down to the papers related to the various PICOT questions.

Each paper retrieved was subsequently reviewed and filtered based on title and abstract by the assigned REG support. At this point RCTs, case studies, cross-sectional studies, reviews or articles related to COPD or allergy were excluded. The remaining papers were reviewed by Nicolas

26th September 2015

December 2015

April - June 2016

October - November 2015

Roche to confirm their appropriateness for inclusion in Phase II.

## Phase Ib: Develop a quality appraisal tool to evaluate the current CER asthma literature (associated with selected PICOT questions)

Five taskforce members, led by Jon Campbell, undertook a pilot test of a beta version of the tool to assess interrater reliability from February to April this year. The tool builds on existing quality parameters outlined by Roche et al and ISPOR and was further revised based on the feedback at a taskforce meeting held at the 2015 ATS.

Wider evaluation of the inter-rater reliability of the QA tool is now underway and is due to complete later in August. 30 participants agreed to be involved, including REG collaborators; taskforce members; members of key guideline committees (GOLD, GINA) and members of the EAACI Asthma Assembly. The team split into three groups of ten, each in receipt of the QA tool and two papers to review.

The assessment will be closed when a minimum of 20 raters have returned their reviews, at which time the rater scores will be combined and analysed for review at the **taskforce meeting planned for Saturday September 26th from 09.30-11.00 in Amsterdam** to coincide with the ERS Congress. At this point, the QA tool will be finalized for use and an assessment of the literature will proceed during October and November with separate taskforce subgroups focussing on different PICOT questions.



#### **TASKFORCE MEMBERS**

**Lead:** Nicolas Roche

**Members:** David Price, Mike Thomas, Eric van Ganse, Guy Brusselle, Jennifer Quint, Jerry Krishnan, Leif Bjermer, Nikos Papadolpoulos, Maarten van den Berge, Jon Campbell.

**REG Support:** Alison Chisholm, Katy Gallop (literature review)

### TIMELINE

Taskforce meeting at the ERS Literature Review Taskforce meeting for initial, raw results review

Final results complete for publication

- \* Learnings conducting systematic reviews of CER
- \* QA tool development
- \* Literature appraisal report

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### The OPCRD – a wonderful real-life research resource!

One of the great benefits of being an REG collaborator is that it grants you free access to the comprehensive UK primary care research database the Optimum Patient Care Research Database (OPCRD). The OPCRD has ethical approval for medical research and contains historical clinical records for over 2 million patients.

To help fuel your research ideas, some key characteristics of the OPCRD are outlined below, e.g. the total number: total number of patients

with physician diagnosed COPD; total number with physician diagnosed asthma, etc.

Following discussions at the recent Biomarkers and Allergy Working Group Meetings in Barcelona in June, a new set of queries has been run, exploring new variables within the database, including the number of patients with:

- Neutrophil counts:
- Both FeNO and eosinophil data;
- InF data

Many thanks to the team at Optimum Patient Care (OPC), particularly Victoria Carter and Derek Skinner, for providing us with this great overview. We are sure you agree that these are impressive numbers and provide great food for thought.

If you have any suggestions for other aspects of the database we can investigate or a research idea, please contact Alison Chisholm alison@ effectivenessevaluation.org) with vour ideas

number, total number of patients	· IgL data.	your lacas.
Category	Patients	Graph
Total	2,292,634	
Asthma Dx. (QoF)	671,801	
COPD Dx. (QoF)	132,962	
C reactive protein	324,530	
Eosinophil Reading	1,317,452	
FeNO	785	
FeNO and Eosinophil reading	575	
Neutrophil	914,206	
Vitamin D level	1,022	
On dual bronchodilators	217,796	
Rhinitis	309,794	
With rhinitis who have FeNO data	306	
Urticaria Dx.	116,628	
immunoglobulin E level (IgE)	17,255	

### Poster Prize for REG at EAACI 2015

We are delighted to have been awarded a poster prize by the European Academy of Asthma and Clinical Immunology (EAACI) Scientific Committee for our poster presentation at the recent EAACI conference in Barcelona in June:

State of the Union – an assessment of current asthmatics, their demographics, treatment and outcomes in 153 practices across

The presentation is available to view on the EAACI Online library. A paper is now in development on this topic. Thanks to all the REG Collaborators who contributed to making this a successful and well-received presentation:

David Price, Wim van Aalderen, Eugene Bleecker, Jon Campbell, Nicolas Roche, Derek Skinner & Victoria Thomas.

### Welcome to our newest Supporters!

We are delighted to welcome three new supporters to the REG network.

Chiesi have pledged their support for a co-funded systematic review and meta-analysis of the comparative effectiveness research associated with small particle ICS therapy.

Kyorin have engaged with us to discuss a range of targeted projects in Japan and we look forward to working on some innovative research projects in this region in the future.

The Adelphi Group have joined the REG Supporter network by pledging support towards the ACOS Working Group.







### New REG website under development

Work has started on the new REG website. The site is being expanded to incorporate the new Working Groups and will also be developed to deliver intuitive navigation and the latest information on REG. The new site will provide a virtual shop window for the organisation and support REG's aims to raise the profile of real-life respiratory research.



If you have any suggestions or ideas regarding the new REG website, please contact Zoe Mitchell zoe@effectivenessevaluation.org.