ADVANCES IN... REAL-LIFE RESPIRATORY MEDICINE

The Respiratory Effectiveness Group Winter Newsletter: Year in Review

Price in print – David reflects on a first exciting year with REG

A time to looking back at 2013 and forwards to 2014...

Management Committee Meeting: Strategic planning in February

The end of the year is always a time of reflection; a chance to look back on what you've done and to make plans and resolutions for the months ahead. This newsletter is a look back at what we, as a group of committed colleagues, have achieved since the launch of REG and to think about what else we should be trying to do in the next 12 months.

So... looking back... What ever was my reasoning for setting up REG...?

Well, RCTs are great. They're very necessary and they have their uses, but they're really the preserve of the regulators. The studies that interest me aren't the ones that address issues of non-inferiority and safety in sanitised patients and practice environments, they are those that try to mimic the world we live and practice in. Real-life studies get at the questions that clinicians, payers and patients really care about. They address *our* concerns about the practical utility and optimum use of licensed therapies.

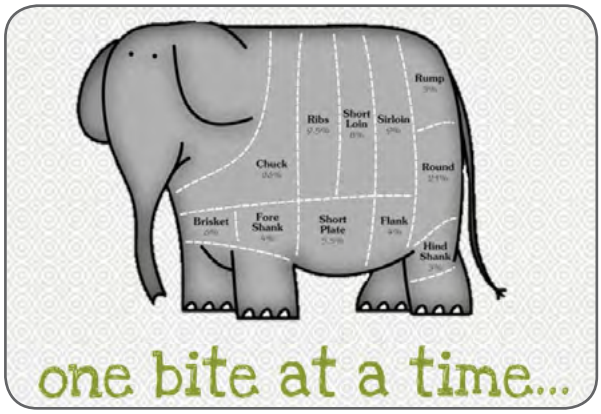
As you know, I've been working in the "real-world" for a good number of years now. I've seen how much the field has progressed in that time and I've also learned a lot along the way about the complexity of real-life study methodologies.

Like me, many of you, see the potential for real-life studies to answer some of the important clinical questions that RCTs fail to address. Between us, we've spent weeks worrying at data... months working on different methods to minimise confounders and we've shed blood, sweat and tears in the pursuit of adding quality data to the existing evidence base. Yet despite the rigour we're imposing on our own work, a few poor quality real-life studies taint the whole field and our data are often greeted with cynicism and dismissed as "data mining" and "fishing expeditions". I got tired of seeing our work passed over by guideline bodies, policy and regulatory decision makers. It was time, I decided, for us to instigate a change. And so REG was born...

On October 1st last year, a rather worried looking Ali turned up for her first day of work and sat at my kitchen table with a blank piece of paper in front of her, wondering how on earth she was going to set about ***improving the quality and profile of real-life respiratory research***. It was certainly a challenging ask, but even a journey of a thousand miles begins with a single step, and our first step was obvious. We needed to invite expert thinkers and clinicians interested in real-life research ("you guys!") to come together to share experiences, identify challenges and start to devise an agenda for change.

This time last year, a dozen or so of you had agreed to come on board as the REG Management Committee to help set the strategy and to break this elephant-sized challenge into digestible and deliverable bites. The wider collaborator group has grown steadily over the intervening year through a combination of word-of-mouth and personal recommendations. We're now an 85-strong group of collaborators from 22 different countries and have kicked off a range of activities in the pursuit of improving the quality and profile of real-life respiratory research. We've also been successful in bringing many of you together at REG meetings around the ATS and ERS. These face-to-face meetings have been the high points of the year for me. When so much expertise and enthusiasm comes together under one roof, the challenges ahead seem infinitely smaller.

I've been impressed, and touched, by your support and enthusiasm...by the numbers of you who turned out at our first nervous meetings; for your proactivity (>60 of you pledging support to the letter of response to the *Blue Journal* – wow!) and for helping to fill Ali's blank piece of paper with exciting and challenging research and advocacy programmes. Please use the pages that follow to congratulate yourselves, but also to help think of gaps in the programme of activities. Your thoughts suggestions and ideas for the future are always welcomed. We're only going to be able to digest this elephant if we all sit down and try to eat him together – Bon Appetit!



The only way to eat an elephant is one bite at a time...

2013 – LOOKING BACK...

REG Structure & Collaborators

Remind us what it's all about – what's REG's central goal?

The central goal of the Respiratory Effectiveness Group initiative is to:
Integrate high-quality, real-life evidence into clinical practice guidelines, policy and budgetary decision-making for the benefit of all stakeholders in respiratory medicine.

And how do we plan to go about that?

REG will achieve its goals by establishing **an international network** of real-life respiratory experts, and by establishing alliances with partner organizations (e.g., EACCI, ERS, ATS, IPCRG, ENCePP) and strategic partners. Together, REG collaborators and partners will implement a multi-faceted programme of activities:

- **Research:** conduct high-quality real-life research that addresses unmet research needs and questions unanswered by traditional randomised controlled trials.
- **Standards:**
  - o Set, publicise, promote and demonstrate high-quality standards for real-life research.
  - o Critically appraising existing real-life respiratory research to:
    - – Identify limitations
    - – Highlight quality evidence available to inform healthcare policy and decision making
- Force a review of existing evidence grading methodologies
- **Education and awareness:** improve the profile and knowledge of real-life research, how to conduct, report, interpret and use real-life evidence.

The REG collaborators are world leaders in respiratory medicine

REG Collaborators (Management Committee Members in bold)			
Alvar Agusti, Spain	Henry Chrystyn, UK	Peter Lange, Germany	Dermot Ryan, UK
Maarten an den Berge, Netherlands	Gene Colice, USA	Federico Lavorini, Italy	Malcolm Sears, Canada
Antonio Anzueto, USA	Alex Dima, Netherlands	Karin Lisspers, Sweden	Sally Singh, UK
Len Bacharier, USA	Michelle Eakin, USA	**Richard Martin, USA**	Iain Small, UK
Vibeke Backer, Denmark	Nemr Eid, USA	**Andrew McIvor, Canada**	Joan Soriano, Spain
Mona Bafadhel, UK	Goran Ericksson, Sweden	**Marc Miravitlles, Spain**	Björn Ställberg, Sweden
Peter Barnes, UK	Daryl Freeman, UK	Ken Ohta, Japan	Stan Szefler, USA
Eric Bateman, South Africa	Andy Griggs, UK	**Nikos Papadopoulos, Greece**	Paolo Tassinari, Venezuela
Allan Becker, Canada	Kevin Gryffudd-Jones, UK	**Alberto Papi, Italy**	**Mike Thomas, UK**
Leif Bjermer, Sweden	Theresa Guilbert, USA	Hae-Sim Park, South Korea	Stephen Turner, UK
John Blakey, UK	John Haughney, UK	Ian Pavord, UK	Omar Usmani, UK
Sinthia Bosnic-Anticevich, Australia	Liam Heaney, Ireland	Stephen P. Peters, USA	Wim van Aaldern, Netherlands
Jean Bousquet, France	Teoh Oon Hoe, Singapore	Wanda Phipatanakul, USA	Thys van der Molen, Netherlands
Andrew Briggs, UK	Janet Holbrook, USA	Hilary Pinnock, UK	Eric Van Ganse, France
Chris Brightling, UK	**Stephen Holgate, UK**	Emilio Pizzichini, Brazil	**Christian Virchow, Germany**
Randall Brown, USA	**Elliot Israel, USA**	**David Price, UK**	Claus Vogelmeier, Germany
Guy Brusselle, Belgium	Christer Janson, Sweden	Todor Popov, Bulgaria	Joergen Vestbo, Denmark
Sonia Buist, USA	Christine Jenkins, Australia	Dirkje Postma, Netherlands	Chen Wang, China
Peter Calverley, UK	Rupert Jones, USA	Cynthia Rand, USA	Andrew Wilson, UK
Jon Campbell, USA	Lynn Josephs, UK	Helen Reddel, Australia	Robert Wise, USA
Niels Chavannes, Netherlands	Alan Kaplan, Canada	Miguel Román Rodríguez, Spain	**Gary Wong, Hong Kong**
George Christoff, Bulgaria	**Jerry Krishnan, USA**	**Nicolas Roche, France**	Osman Yusuf, Pakistan
			NS Zhong, China

2013 – LOOKING BACK...

REG Structure & Collaborators (continued...)

What about outside the REG collaborators group – what patnerships are we working on?

We don't want to duplicate the work of other organisations. REG aims to partner with organisations with aligned goals and to unite existing activities under a common banner. So far, REG has established a number of partnerships:

- The **European Medicines Agency** (EMA) through **ENCePP** (European Network of Centres for Pharmacoepidemiology and pharmacovigilance). REG is endorsed as an ENCePP network and REG studies are pre-registered on the ENCePP e-registry.
- The **International Primary Care Respiratory Group's** (IPCRG's) **UNLOCK** Committee. REG and UNLOCK will host a joint real-life research symposium at the 2014 ERS.
- **Research in Real Life** and **Optimum Patient Care** are strategic partners who offer free access to research quality UK clinical data and data analysis and statistical consultancy and support.

Teva have been a key strategic partner, providing funding support for the first year of the initiative. Boheringer Ingelheim have also pledged their future support for the initiative and AstraZeneca have come on board in the last week. Partnership talks are underway with several other pharmaceutical companies.

Quality Standards: EAACI/REG Taskforce to critically appraise the evidence

Background

In 2008 Sir Michael Rawlins (then Chair of the UK's National Institute for Health and Clinical Excellence) went on record saying: "*Randomised controlled trials (RCTs)... have been put on an undeserved pedestal... they should be replaced by a diversity of approaches that involve analysing the totality of the evidence-base.*"

This sentiment has been reiterated and echoed by Rawlins and others in the years since. Some groups and societies have also published statements calling for the use of more patient-centric outcomes, composite measures and a diversity of study designs to address the questions (and to reflect aspects of disease) that have not been addressed by RCTs.Yet calls for action haven't yet translated to real action. One reason for this may be the lack of clear guidance on how to go about changing evidence appraisal to integrate non-RCT evidence streams. The traditional hierarchical view of evidence (with RCTs at the top) is so imbedded in the psyche that it takes time, concerted effort and the provision of enabling tools to revise it.

Many of the respiratory guidelines bodies currently use the GRADE approach to evaluate evidence. There are merits to GRADE, but there are also inherent limitations. For example, GRADE requires PICO questions to be asked – questions so specific that their answers are not generalisable to the vast majority of patients treated in routine care. GRADE's quality classifications results in most evidence from real-life studies being dismissed as unworthy of consideration by guideline developers.

While there needs to be quality control of evidence, there is also a need to recognise that different study designs must be called upon to answer different types of questions and that where RCTs cannot (or have not) addressed all the important questions faced by the practising physician, other sources of evidence may have value.

Changing evidence evaluations

It has become increasingly apparent that if we, through REG, want to see valuable, high-quality real-life research incorporated into guidelines, we have to provide the tools and the methodologies for facilitating that change. That means we have to develop tools to assist in a reappraisal of the evidence base, devising quality standards for carrying out research and also methods for evidence integration. REG's published correspondence in December's *Lancet Respiratory Medicine* (see p4) was a **first step** towards positioning real-life studies (both observational studies and pragmatic trials) within the same space as RCTs – a space defined by a "study population" axis and a "management approach" axis. The **second step** will be the publication of REG standards and checklists for preparing data for, conducting and reporting observational studies. The paper will appear in an REG *ATS Annals* supplement to be published in February next year (see p4)...

EAACI – the next step

The **next step** will be the development of quality assessment scoring tools and testing of those tools through a systematic review of the published real-life literature. This challenge (with a focus on asthma) is the objective of the recently confirmed EAACI/REG Taskforce.

EAACI's recognition of the importance, and support, of the development of real-life evidence quality assessment tools is an important step forward. So too will be the final Taskforce publication – a critical review of the existing real-life asthma evidence.

2013 – LOOKING BACK...

Publications: review papers, position papers, letters to editors

What have we shared with the world beyond REG in 2013?

We can do and say what we like, but unless we get the message to the outside world, our ideas won't travel.

Many REG collaborators have committed substantial time and effort to putting pen to paper and formalising the discussions from the various REG meetings held in 2013. Several pieces have been submitted and accepted for publication and have either *just been published*, or will *appear in print early in the New Year*.

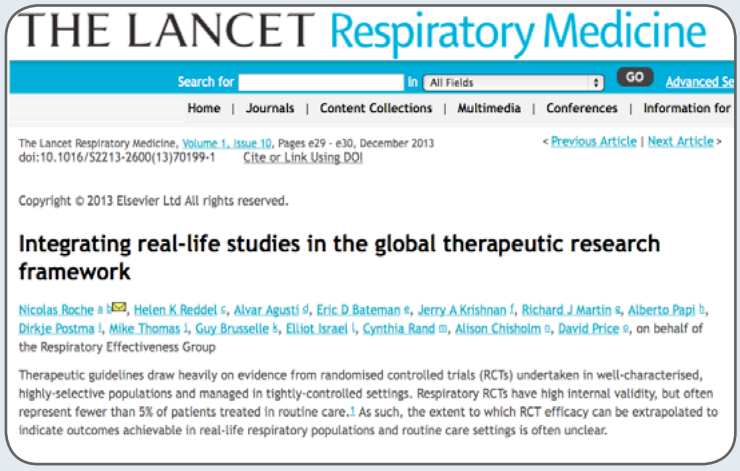
Ending 2013 with a publications blast!

Lancet Respiratory Medicine

Roche N, Reddel HK, Agusti A, Bateman ED, Krishnan JA, Martin RJ, Papi A, Postma D, Thomas M, Brusselle G, Israel E, Rand C, Chisholm A, Price D. Integrating real-life studies in the global therapeutic research framework. Lancet Respir Med, 2013;1(8):30–32

At the REG Collaborators' Meeting at the ATS, we discussed the need to integrate real-life research into the global research framework, and to provide an alternative to the traditional hierarchical view of evidence.

A unified framework was proposed by Nicolas Roche, Helen Reddel and David Price (in no particular order) and further developed by a lager group of coauthors over the following weeks. The framework defines a two-dimensional space in which all studies (RCTs, pragmatic trials and observational studies) can be positioned relative to each other. The space defined in the paper is bound by a y-axis representing the "study population continuum" running from *highly-selected RCT population* at the intersection of the axis to a *managed care* population at the other end. Along the x-axis runs a "management approach (or ecology of care) continuum" with *highly-controlled management and follow-up* at the intersection of the axes to *observational* at the other. Positioning studies within the framework helps to illustrate where they sit relative to each other in terms of the degree to which they reflect real life. Neither aspect alone is sufficient to quantify this. The position of a study is not a marker of quality, rather a means to understand where a study "fits" and to identify the appropriate quality assessment tools.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Integrating real-life studies in the global therapeutic research framework

Nicolas Roche a, Helen K Reddel c, Alvar Agusti d, Eric D Bateman e, Jerry A Krishnan f, Richard J Martin g, Alberto Papi h, Dirkje Postma i, Mike Thomas j, Guy Brusselle k, Elliot Israel l, Cynthia Rand m, Alison Chisholm n, David Price o, on behalf of the Respiratory Effectiveness Group

Therapeutic guidelines draw heavily on evidence from randomised controlled trials (RCTs) undertaken in well-characterised, highly-selective populations and managed in tightly-controlled settings. Respiratory RCTs have high internal validity, but often represent fewer than 5% of patients treated in routine care.1 As such, the extent to which RCT efficacy can be extrapolated to indicate outcomes achievable in real-life respiratory populations and routine care settings is often unclear.

The Blue Journal (AJRCCM)

Price D, Roche N, Martin RJ, Chisholm A. "Feasibility and Ethics". American Journal of Respiratory and Critical Care Medicine, 2013;188:1368-1369.

This letter was REG's collective response to a damning view of observational studies published in the Blue journal in the summer. The original review, written by Dr Albert and titled: ***Lies damn lies and observational studies*** (citation: AJRCCM, 2013;187(11):1173-7), accused observational studies of being, at best unnecessary, and at worst potentially harmful. Dr Albert dismissed their utility in favour of RCTs, which he argued, can be designed to answer almost all research questions.

The REG letter of response argued that there *is a need* for observational studies in certain scenarios, particularly where there are challenges around *Feasibility & Ethics* (the title of the letter) of designing RCTs. Thank you to Nicolas Roche and Richard Martin who both drew our attention to the review and for their work in drafting the letter. Thank you also to the 40+ collaborators who pledged their support of the letter – your names appear in the December issue's online supplement.

Starting 2014 in style

In February, REG will have a second publications blast. Not only will there be a review paper published in *Allergy, Asthma & Immunology Research* (AAIR) considering how real-life evidence could be integrated into clinical management decisions for asthma patients who smoke (coauthored by Todor Popov, Leif Bjermer, David Price and myself), but the REG Arch Summit Supplement will also appear in print.

The real-life themed *Annals of the American Thoracic Society* supplement will bring together many of the ideas and concepts discussed at the REG Management Committee in February this year. We hope it will tell a story through the papers it includes.

The first piece will be an introduction to REG and our aims and ambitions. The second will take a look at the value and limitations of RCTs, at how guidelines use evidence and, as a consequence, the limitations of guidelines that drawn only on RCT data.

Having argued that there are clinical challenges that lie outside current guideline recommendations, the third paper goes on to look at how real-life studies (both observational studies and pragmatic trials) have the potential to "plug some of the gaps".

The very necessary third paper then acknowledges the limitations inherent in real-life studies and signposts guidance for pragmatic trials design and the reporting of real-life studies.

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It offers a series of recommendations (with associated checklists) for conducting observational studies (data preparation, management and publication).

The following three papers move away from these general conceptual papers to look more specifically at scenarios in which real-life studies have particular potential – in cost-effectiveness evaluations of therapies; in better capturing patient-centred data (and how to bring the patient more into meaningful research), and in the post-marketing environment as Phase IV implementation studies.

The supplement will be published online only (open access), but we will buy a number of hard copies to have as physical aids to promote the spectrum of ideas presented. Each paper will be downloadable uniquely, not only as part of the supplement. A huge thank you to all the coauthors who have given their time so generously and who have worked so effectively to make an ambitions project (relatively!) straight forward.

What's next?

David's recently received a new commission to write a paper on the implications of different types of ICS therapies in real-life... there is an intention to build on the integrated research framework published in the *Lancet Respiratory Medicine* with a longer systematic review... Vibeke Backer, Alan Kaplan and Helen Reddel have started work on recommendations for routine care data capture that would help with identifying true asthma patients within clinical practice datasets... a *JACI* supplement is a possible future goal, although perhaps one for 2015/6.

We welcome other publication ideas. The more noise and spotlights we can shine on specific issues, the harder it will be to ignore the presence of real-life research.

Communications: congress sessions

Successes

The 2014 ERS Annual Congress' Scientific Programme will include a symposium proposed by REG in collaboration with the IPCRG's UNLOCK group, title: ***The evolving role of real-life research in respiratory medicine.***

The UNLOCK group and REG have a strategic partnership. UNLOCK is a group, or network, of International Primary Care Respiratory Group (IPCRG) members who have access to a variety of asthma and COPD databases – some are trial databases, some cohort study databases, others are routine clinical databases. UNLOCK are mapping data fields across these databases to enable studies to be validated and queries rolled out across multiple databases.

Although the scope of UNLOCK and REG differs, many of our core principles are aligned and we have a strategic partnership to co-support each others activities.

The joint REG/UNLOCK session titles proposed include:

- Real-life studies – a poor relation or important partner to the respiratory RCT
- The implications of real-life (comorbid conditions, inhaler technique and lifestyle factors) on asthma management: is there any evidence available?
- Developing and applying datasets and standards for high-quality real-life research
- Phase IV implementation studies: the forgotten finale to the MRC framework

Failures

There were a number of other congress symposium applications submitted this year that weren't quite as successful. We sent in applications to the ERS (for the 2013 congress), to the IPCRG, to Chest and to EAACI 2014, all of which failed to be accepted or shortlisted. The absence of US and Rest of World conferences on this list of submissions purely reflects our naivety around the lead times involved in conference planning and that other relevant deadlines had already hurtled past before we knew it. Armed with a little more awareness, we hope to submit applications next year for all the key 2015 international congresses.

We expect there are a number of reasons for our limited success with conference session applications . One is that some of our applications came late in the development of the respective society's planning and didn't "fit" with the general congress programme. Another is that although real-life research is increasingly spoken of, it still sits on the sidelines of academic programme planning (if it were, REG's work would be done!). Our lack of success is a reminder that REG's work is not only important but necessary to change this view of the field. We'll keep sending in those applications!

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REG Research Programme: initial plans

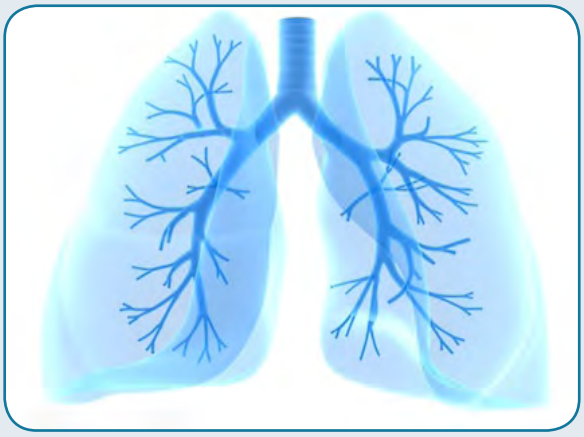
If REG is going to be more than a discussion group, it needs to undertake its own research

On day 1 of REG, we knew that research would need to be a core element of the initiative. This was quickly confirmed by the early collaborator email exchanges in which it was noted that:

"*If REG is going to be more than a discussion group, it needs to be undertaking its own research, demonstrating expertise, addressing important research questions and building a platform for future advocacy work.*" (Agreed)

Our initial thinking had been to conduct ~3-4 studies a year:

- A validation or methodology study to work towards best practice standards for observational research;
- A study that tests a guideline recommendation in a routine care population (a way to validate, or challenge existing guidance)
- A study that addresses a research question close to the hearts of the REG collaborators
- A study that would involve collaboration across chronic disease specialties such as diabetes to learn from the research experiences of non-respiratory clinicians and to start to build a "multidisciplinary real-life network".

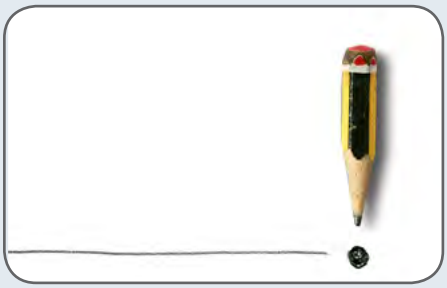


The Management Committee were quick to recommend we "stick to what we know" and so thoughts of forging links outside of respiratory medicine were set aside (at least for now). Instead we brainstormed important research topics and built an initial research needs list (see the REG website under "Research"). A number of these floated to the top and became our year 1 research priorities.

Each REG-funded study has its own working group, formed of REG collaborators who have volunteered their time and expertise because of their interest in the topic. So far, the working groups have been involved in protocol review and revision and will be brought together (either virtually or face-to-face) to review the data, advise on re-analyses, and to interpret the findings for publication. In recognition of their contributions, REG collaborators participating in the studies will be recognsied as co-authors on all study-related publications.

REG Research Programme: realities – *funded* research

Asthma endpoint validation study



Asthma endpoint validation study

Publication of observational studies is challenging for a number of reasons, among which is the lack of standardised, agreed and validated outcomes. This REG study is a first attempt to "validate" a number of asthma endpoints that have been used in published observational asthma studies; to compare them to patient reported outcomes and RCT tools; to assess their internal validity, responsiveness to therapy and, where appropriate, the extent to which they are predictive of future risk.

Status: The study protocol was approved by the Optimum Patient Care Research Database's (OPCRD's) ethics committee (ADEPT) in the spring and is registered on the ENCePP e-study registry. Early data from the study were presented at the REG collaborators meeting at the ERS in September. The remaining analysis is currently underway and should be complete in January. A number of REG collaborators are involved as an expert steering group.

Collaborators involved: Richard Martin (PI), David Price, Alexandra Dima, Elliot Israel, David Price, Gene Colice, Todor Popov, Janet Holbrook, Emilio Pizzichini, Nikos Papadopoulos, Guy Brusselle, Helen Reddel.

Asthma risk predictors study

Control has been the holy grail of asthma management for many years, but increasing thought is being given to the potential benefits of risk stratification in asthma.

There appears to be a subgroup of patients who exacerbate frequently. The aim of the REG study is to better understanding what these patients "look like" and what identifying markers of this trait might be detectable from routine practice data.

The goal is to develop risk scores that will assist in better identification of patients at risk of future exacerbation with a view to modifying that risk.

Status: the study protocol has been finalised and approved by the OPCRD's ethics committee and is registered on the ENCePP e-study registry. Identification and extraction of the dataset began the week commencing 25 November.

Collaborators involved: Mike Thomas (PI), Ian Pavord, Alan Kaplan, Dirkje Postma, David Price, Cindy Rand, Gene Colice, Alberto Papi, John Blakey, Lynn Josephs, Todor Popov, Janet Holbrook, Hilary Pinnock, Iain Small, Emilio Pizzichini, Alexandra Dima, Vibeke Backer, Samantha Walker, Borislav Dimitrov.

COPD and blood eosinophils

Although eosinophilic airway inflammation is usually considered a feature of asthma, it has also been demonstrated in large and small airway tissue samples taken from patients with COPD and in 20–40% of induced sputum samples from patients with stable COPD. Bronchial biopsy have also shown that, compared to levels in stable COPD controls, airway eosinophils increase significantly during COPD exacerbations. Against this background, the aim of this study is to use primary care clinical records

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to explore the relationship between blood eosinophil count and future exacerbation risk in COPD and the effect of preventative COPD therapy on eosinophil level. Additional analysis will also aim to investigate the stability of the phenotype, defined by change in eosinophils over time and in response to treatment.

Status: the study protocol has been finalised and approved by the OPCRD's ethics committee and is registered on the ENCePP e-study registry. Early exploratory data were presented at the ERS in September, but identification and extraction of the full study dataset is now underway with early results expected in January.

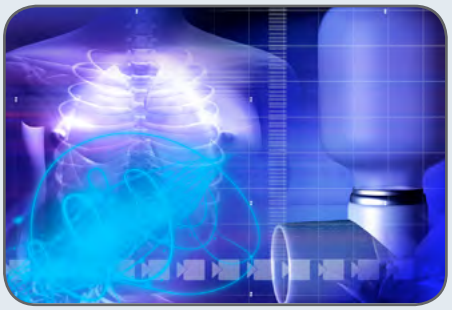
Collaborators involved: David Price (PI), Alvar Agusti, Antonio Anzueto, Ian Pavord, Claus Vogelmeier, Nicolas Roche, Dirkje Postma, Todor Popov, Daryl Freeman, Dermot Ryan, Rupert Jones, Emilio Pizzichini, Alberto Papi.

Adherence:

The (bi-directional) relationship between therapy adherence and asthma outcomes

Important questions remain about asthma adherence – do high levels of adherence result in well-controlled disease? Do they moderate asthma outcomes? Do they reflect higher medication dependence because of poorly-controlled disease?

If patients self-manage in routine care based on perceived medication need, high levels of adherence may reflect high medication dependency and poorly-controlled disease. The aim of the study is to utilise a routine care dataset that is devoid of the artificial adherence controls imposed in RCTs to explore to what extent (and in what contexts) adherence may be considered an asthma outcome, and/or a predictor of asthma outcomes by



investigating the bi-directional relationship between database markers of asthma treatment adherence and asthma control.

Status: protocol development is well advanced and the protocol will been finalised before the end of the year.

Collaborators involved: Gene Colice (PI), Michelle Eakin, Alexandra Dima, Cynthia Rand, Iain Small, Miguel Roman Rodriguez, Janet Holbrook, Janet Holbrook, Randall Brown, Nemr Eid, Eric van Ganse, David Price.

REG Research Programme: realities – *supported* research

Paediatric Step-up

The aim of the study, led by Steve Turner at the University of Aberdeen, is to use an observational dataset to explore the:

- Pattern of step-up prescribing in paediatrics
- Comparative outcomes associated with different step-up options
- Implications of switching children with asthma between ICS inhaler devices.

Status and REG's involvement: The study has been jointly funding by REG & Research in Real Life Ltd (RiRL). The data is extracted and the baseline analysis is now complete. Early outcome data are expected in February 2014. An REG working group is being brought together to work with Steve to review and interpret the data and to progress it to publication.

Confirmed collaborators involved: Steve Turner (PI), David Price, Mike Thomas, Alan Kaplan, Stan Szefler.

The health care costs associated with comorbidities of refractory asthma and systemic steroid exposure in the UK

Using observational data, the prevalence of comorbidities and new incidence of comorbidities in patients on long-term oral steroids will be compared to (age-, gender- matched) controls with the goal of developing cost models to estimate the financial burden associated with refractory asthma and management of steroid-induced morbidities.

Study origin, status and REG involvement: The study was brought to REG by Liam Heaney and his team at University College Belfast. REG has supported the ethical review and approval of the protocol and provision of the dataset for analysis. The dataset was sent to the Belfast team for analysis in November.

Cardio- and cerebrovascular risk associated with nicotine replacement therapy (NRT)

David was approached to repeat an exploratory study conducted by a Scandinavian team that suggested there may be a cardiovascular risk signal associated with use of nicotine replacement therapy. David has been pursuing a repeat study using the UK's Clinical Practice Research Datalink through his company Research in Real Life since 2010 (with data provided through a grant from the UK's Medical Research Council). Data highlights from the study were presented at the ERS.

Status and REG's involvement: The study has been completed with the support of REG as a co-funder. An REG working group is now in place to review the data and progress it to publication.

REG collaborators involved: David Price (PI), Emilio Pizzichini, Marcia Pizzichini, Alan Kaplan, Richard Martin, Joergen Vestbo, Tarita Murray-Thomas.

The effect of the use of statins ± beta blockers on exacerbation frequency in patients with COPD

Using observational data, the study aims to determine the frequency of exacerbations and all-cause mortality associated with use of statins, beta blockers or statins *and* beta blockers in patients with COPD. Subgroup analyses will explore effects of the drugs on patients who have frequent exacerbations, and the affect across patients of different dose score.

Study origin, status and REG involvement: Andrew Wilson and colleagues at the University of East Anglia developed the protocol and will be carrying out the analysis. A dataset for the study was provided through REG in October.

2014 – LOOKING FORWARD...

Introducing more structure to the initiative

Moving away from purely organic growth and towards a more strategic and transparent way forward

When we set REG up, it made sense to let it grow organically – to see what worked and what didn't. Now, a year in, it's time to introduce a little structure, clarity and ensure transparency around the running of the initiative. 2014 changes will include:

- Introduction of a clear constitution so we have transparent processes ("a must" for several potential spnosors we've spoken to). This is currently under development, but will be published early in the new year.
- Specific role allocation within the Management Committee so we have regional leads and topic-specific leads who will become the "hubs" for feeding information and ideas from their region or speciality area into the initaitive. Like the constitution, this work is underway and the new structure and role allocation will be announced the new year.
- A Research Planning System.

Research Planning tool

When REG was launched, David was already brimming with research questions and ideas that REG was be well-positioned to answer. These ideas were discussed, expanded and added to at the REG Management Meeting in February and a number of initial research questions "bubbled to the top". These have formed the backbone of the REG research programme over the last 12 months.

Other collaborators have approached us throughout the year to requested use of the Optimum Patient Care Research Database (OPCRD) for their own studies – studies with some degree of protocol already developed and where there has been a team available to carry out the analysis. In these instances, REG has helped get the protocols approved by the OPCRD ethics committee and has supplied a dataset for analysis.

This approach has been reasonably successful, after all, we now have a number of important studies underway (see pages 6–7). However... going forward, we will be taking a more structured approach to research planning and prioritising by developing a planning tool that will allow everyone to upload their own, and review others', research ideas in one central location. The ideas will then be reviewed (by an REG review committee) and prioritised for REG funding to make sure the ideas that address the greatest unmet need are prioritised for funding.

The idea isn't to create bureaucracy, rather to establish a way for everyone to input into the research planning process, and to highlight the priority ideas. We've just started work on an online platform where ideas can be logged and viewed by everyone. We hope to launch it early in the new year.

Do start thinking of the projects and questions you'd like to address as well as the best study design to address that question... primary endpoints... comparator therapies, etc.

A quick look at the REG Research Needs page might help get those ideas flowing – go to the REG website: **www.effectivenessevaluation.org**, click on the "**Research**" tab at the top of the page and then on "**Research Needs.**"

2014 research ideas proposed so far...

Longitudinal study of asthma treatment patterns and related outcomes

Concept: Many studies look at the British Thoracic Society (BTS) or Global INitiative for Asthma (GINA) treatment step as a static / cross-sectional exposure. It may be possible to learn much more from a dynamic / longitudinal study of treatment transitions (i.e. step up / step down) and how these influence outcomes. A dynamic treatment pattern study could also be used to help with better position of new (and existing) products.

Linked to REG published research need: Utilize real-life longitudinal data to map treatment pathways and response rates for different therapies to offer guidance on potential sequential treatment options.

Outpatient factors predictive of emergency department use and hospitalisations among patients with COPD

Concept: explore factors among outpatients with COPD that predict ED use and hospitalisations for respiratory-related illness (e.g. pulmonary rehab, COPD phenotype and GOLD status).

Linked to REG published research need: Evaluate the interaction of treatment interventions, outcomes and phenotype.

Comparative effectiveness of fixed dose combination ICS/LABA vs triple therapy in COPD

Concept: To use routine clinical data to compare the effectiveness of triple therapy (ICS+LAMA+LABA) vs fixed dose combination ICS/LABA therapy in real-life patients, primarily in terms of its impact on COPD exacerbations, but also in terms of its effect on rescue medication and association with COPD phenotype.

Linked to REG published research need: Utilize real-life longitudinal data to map treatment pathways and response rates for different therapies to offer guidance on potential sequential treatment options.

Validation work around the RCP3 questions

Concept: To use routine clinical data to test the validity of the RCP 3 questions.

Linked to REG published research need: Validate real-life study endpoints against existing "gold standard", e.g. asthma control, as evaluated in observational studies against the ACQ, ACT, AQLA.

Studies to further explore the utility of real-life studies in informing meaningful health economic modelling.

2014 – LOOKING FORWARD...

Funding: opportunities for private & public support

REG is an independent organisation, run by the collaborators for the common good. As a not-for-profit social enterprise, REG has a **social mission** at its core. To date, our activities have been support by a number of sources:

- **Private support:** Financial support from Teva and AstraZeneca and a pledge of support form Boehringer Ingelheim.
- **Research in Real Life & Optimum Patient Care:** support from David's for-profit & not-for-profit companies in the form of cost-price data analysis and statistical support, and free use of the Optimum Patient Care Research Database.
- **Society Support:** The European Academy of Allergy and Clinical Immunology (EAACI) through provision of taskforce approval and support to conduct a critical appraisal of the real-life asthma evidence base.

We are in discussions with several other potential private sponsors, but we also want to look at public funding opportunities, and welcome your thoughts and suggestions.

Funding avenues flagged so far?

A number of potential funding sources have been suggested by collaborators so far, including:

- UK National Institute for Health Research
- The US Patient Centred Outcomes Institute (PCORI)
- European Commission's Horizon 2020
- The Bill & Melinda Gates Foundation
- National Heart, Long and Blood Institute (NHLBI) of the National Institute for Health (NIH) in the US.
- Conferences and charities

We'll look into these opportunities in the new year. If you have other thoughts and ideas for potential sources of funding, please contact Alison.

Supporting grant applications

The remit of REG is to improve the integration of "real-life" research into clinical guidelines, policy and decision making, with "real-life" being an umbrella term for both observational studies *and* pragmatic trial work.

REG's pockets are not currently deep enough to fund a pragmatic trial, but... we *can support* pragmatic trial work by conducting observational analyses to help support grant applications for pragmatic trials (e.g. feasibility assessments; population characterisation, etc). For example, some work was carried out by REG in November to look at predictors of asthma-related hospitalisation to support an application to the UK's Health Technology Assessment for developing At-risk Registries.

Webinars

The time between submitting a congress abstract and the congress itself is often 5–7 months. When congresses finally arrive, there is seldom enough time to really discussion the results and the methodological learnings in depth.

REG will be looking into pioneering regular webinars to present abstracts and then allow 20–30 minutes to discuss the data and its methodological implications. This fits with REG's goal of educating and improving research standards and methods.

REG Summit Announced!

27–29 June in London (dovetailing with COPD9)

Short (2-hr) REG meetings around other conferences is a great way to maintain momentum and to discuss a limited number of topics, but it's not enough time to present in-depth research findings or to have detailed discussions. So... in 2014 REG will be holding a 2-day event—a "Real-Life Summit"— in London from the **28–29th of June** (immediately following the COPD9 Conference in June, Birmingham). As the COPD9 meeting finishes at lunchtime on the 27th in Birmingham, the main REG event will commence on the 28th, but *some sessions* will be held on the afternoon of the 27th.

Now a date is fixed, Alison will be looking into venues. At this time, a *central London* location seems likely, but more information will follow in the new year.

Possible Agenda Items

Some session/symposia slots will be offered to REG sponsors and some time will be set aside to discuss REG business issues. However, the main programme will include a mixture of research, methods and quality standards sessions; plenty of time will be left for discussion and debate.

Programme ideas suggested so far (by the Management Committee) are detailed below, but this is **your conference** so please send your programme ideas and session suggestions to Alison:

- *Taskforce activities*
  - Presentation of the EAACI taskforce work (taskforce launch date Jan 2014)
  - A review of the process requirements for a joint ATS/ERS/EAACI taskforce proposal.
- *Leveraging new datasets*
  - Discussion of the UNLOCK group's experiences and learnings from trying to combine and validate research across multiple different national databases.
  - Presentation about the recently announced PCORnet project in the US – a $93.5 million project funded by the Patient Centred Outcomes Research Institute (PCORI) to develop a US national network to support more efficient patient-centred research.
  - Presentations from representatives of other databases.
  - E-datasets: harnessing new technologies to generate innovative datasets.
- *Methodology sessions*
  - Invite experts working in observational and comparative effectiveness research outside the Pulmonary community to share their expertise.