REG COLLABORATORS' MEETING REPORT

SUNDAY 8TH SEPTEMBER 2013, THE EUROPEAN RESPIRATORY SOCIETY CONGRESS IN BARCELONA

Respiratory Effectiveness Group Collaborator Meeting

Date: Sunday the 8th of September, 2013
Venue: Room 4.4B, Convention Centre 4, Fira Barcelona
Timings: 9:00–11:00 (breakfast & refreshments will be available)

Meeting Agenda

9:00–9.15: Welcome & Update
– David Price, REG founder & Alison Chisholm, REG Director

9.15–9.45: Research: new data highlights
• **Study progress updates: COPDGene / Adherence / Risk Predictors**
– Richard Martin, National Jewish Health / Gene Colice University School of Medicine / Mike Thomas, University of Southampton
• **Blood eosinophil levels in real-life asthma and COPD**
– Lead Investigator: David Price, University of Aberdeen, Aberdeen, UK
• **Smoking Cessation and cardiovascular risk**
– Lead Investigator: David Price, University of Aberdeen, Aberdeen, UK
– REG Statistician: Annie Burden, Research in Real Life Ltd, Cambridge, UK
• **Real-life asthma endpoint validation**
– Lead Investigator: Richard Martin, National Jewish Health, Denver, Colorado, USA
– REG Statistician: Annie Burden, Research in Real Life Ltd, Cambridge, UK

9:45–10.00: REG quality standards work – highlights
Nicolas Roche: Hôpitaux Universitaires Paris Centre, Paris, France
GROUP DISCUSSION: A STANDARDS WORKING GROUP? PUBLICATION & ACTIVITY NEEDS

10:00–10.30: Working with guideline bodies – how might real-life data be incorporated
Eric Bateman: University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa
GROUP DISCUSSION: GUIDELINE ENGAGEMENT AND NECESSARY ADVOCACY ACTIVITIES

10:30–11.00: Open ideas session:
• **10.30–10.40: 3CIA initiative – CONCEPT**
Joan Soriano, Bunyola, Illes Balears, Spain
• **10.40–10.50: ASTROLAB**
Eric van Ganse, Lyon, France
• **10.50–11.00: A new working group – the role of pragmatic RCTs in establishing the effectiveness of complex interventions**
Eric Bateman, Capetown, South Africa

Objectives & Report Index

Publications and Communications Update

After David welcomed the ~50-strong REG collaborators to the meeting, Alison began discussions with an update on the various communications-related activities that REG has underway:

Abstracts

REG had two posters being presented at the 2013 ERS Congress.

The abstracts were authored by the members of the REG Management Committee who wrote and reviewed them when they met in February this year: Richard Martin, Marc Miravitlles, David Price, Jerry Krishnan, Leif Bjermer, Gary Wong, Jonathan Campbell.

The abstracts aim to highlight: (i) The need to explore outcome measures to ensure they are meaningful, and (ii) The role real-life studies can play in exploring features of disease in subgroups typically excluded from RCTs.

Poster 1: Excess inhaled corticosteroid adherence may be a marker of uncontrolled asthma: the poster presents data showing that >100% adherence to inhaled corticosteroid (ICS) therapy is associated with lower odds of achieving asthma control and higher rates of adherence, posing the question: is adherence an outcome or a marker of severity?

Poster 2: Real-life Asthma Impairment: SABA use depends on smoking phenotype: the poster presents data on short-acting bronchodilator (SABA) use in smoking asthmatics vs patients who are ex- or non-smokers. Smokers were found to use significantly higher doses of SABA and to be more resistent to ICS.

Publications & Communications Activities Update

Congress Activities

European Respiratory Society Annual Congress, Munich 2014: REG and the International Primary Care Respiratory Group's (IPCRG's) UNLOCK Committee (www.theipcrg.org) joined forces in March and submitted a joint session proposal for the 2014 congress, entitled: **"The emerging role of real-life research in respiratory medicine."** The proposal was accepted, so real-life respiratory research will feature as an integrated part of the ERS's main scientific programme in 2014!

Manuscripts

Review papers: REG will be publishing a series of reviews and editorials throughout the initiative to help to raise awareness of key issues in real-life respiratory research, to promote best practice, and to help educate the wider community.

Most recently (and in response to a commission from the journal), a review article has been authored by David Price, Leif Bjermer, Todor Popov, Alison Chisholm and submitted to the journal *Allergy, Asthma & Immunology Research* (AAIR). The title of the paper is: "Appraising the integrated evidence base for managing asthma in patients who smoke."

Letter of correspondence to the Editor of the Blue Journal: REG wrote a letter of correspondence to the Editor of the American *Journal of Respiratory and Critical Care Medicine* (AJRCCM) following a review published in the journal titled: "Lies, Damned Lies..." and Observational Studies in Comparative Effectiveness Research" (Albert RK, 2013;187:1173-7). The letter was authored by Richard Martin, Nicolas Roche, David Price and Alison Chisholm and endorsed by >60 REG Collaborators. The letter was accepted and is currently in press.

Research papers: All REG-funded studies will be submitted to peer review respiratory journals when complete.

Research framework for Lancet Respiratory Medicine

A new framework for classifying research was devised during discussions at the REG Collaborators' Meeting that was held at the 2013 American Thoracic Society Congress. The framework was driven by the need to classify research appropriately depending on the degree to which its design reflects "real-life". Only when: (i) the **study population** is well described (e.g. highly selected, spirometry-diagnosed COPD vs "managed as"

Supplement to Annals of the American Thoracic Society

"Arch" reflects the venue of the Committee Meeting & REG's goal of spanning and linking international experts and research expertise.

Concept: Proceedings of the REG "Arch" Management Committee Meeting held in London in February 2013. The supplement will be a landmark publication including an executive summary (introducing REG, its motivation, goals and objectives) and by six papers that address different challenges, opportunities and considerations associated with real-life respiratory research:

- Guideline development and gaps in the evidence base;
- How real-life studies can help to plug the gaps in the RCT evidence base;
- Quality standards & benchmarking criteria for real-life research;
- Integrating different stakeholder perspectives:
  – The patient perspective; The payor perspective
- Utilising real-life studies as implementation studies for complex interventions

International author list: Richard Martin, David Price, Gary Wong; Jerry Krishnan; Marc Miravitlles, Eric Bateman, Nikos Papadopoulos, Sinthia Bosnic-Anticevich, Sonia Buist, Emilio Pizzichini, Nicolas Roche, Helen Reddel, Guy Brusselle, Alberto Papi, Mike Thomas, Dirkje Postma, Alexandra Dima, Cynthia Rand, Jon Campbell; Andy Briggs, Robert McQueen; Susan Bartlett, Teresa Barnes, Andrew McIvor; Hilary Pinnock; Eleni Epiphaniou; Stephanie Taylor.
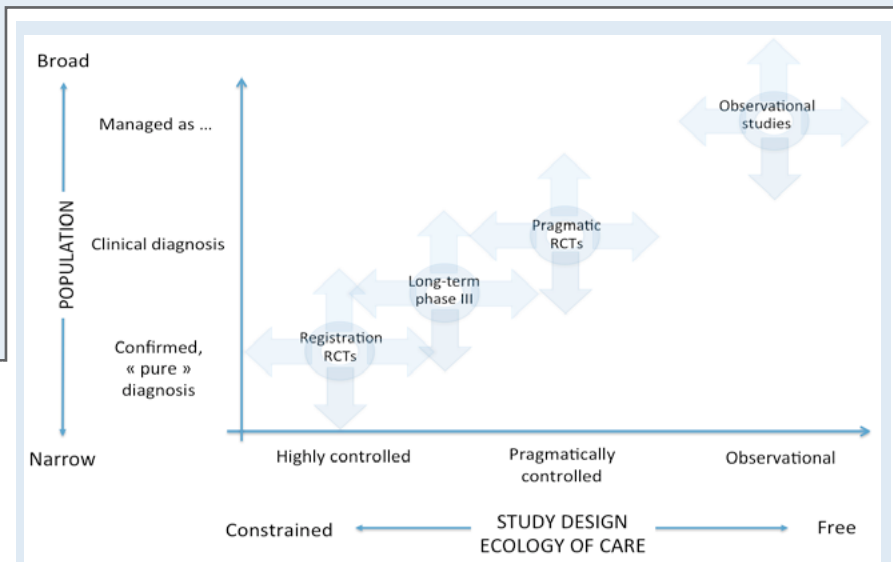
COPD) and (ii) the l**evel of intervention** is appropriately described (e.g. highly-interventional vs observational) can the relevance of the results be understood in relation to the target population. *See page 7 for further detail.*

The *Lancet Respiratory Medicine*'s Editorial Office has expressed interest in the piece as a Comment. The paper was being finalised for submission at the time of the Collaborators' Meeting. **Authors:** Nicolas Roche, Helen Reddel, Alvar Agusti, Eric D Bateman, Jerry Krishnan, Richard Martin, Alberto Papi, Dirkje Postma, Mike Thomas, Guy Brusselle, Elliot Israel, Cynthia Rand, Alison Chisholm, David Price.

Update on REG's Year 1 Research Activities

The second session of the meeting was a Research Update Session, designed to give a top-line overview of some of the research work that REG has planned, or is already underway. Preliminary data were presented on three studies – "Asthma endpoint validation study"; "Blood eosinophils in COPD" and "Nicotine replacement therapy and cardiovascular risk". Slides of the presented data can be accessed through the REG website (visit Research and Activities>>Presentations & Events then select ERS 2013: REG Collaborators' Meeting and enter the password Barcelona).

REG research background: Part of changing the environ-ment for real-life research is to lead by example by undertaking high-quality research that addresses important unmet research needs. With this in mind, REG plans to fund at least 4 important studies each year. The study topics are selected by the REG Management Committee, or are championed by individual collaborators. REG collaborators are then invited to note their interest if they would like to be part of a study working group. Research ideas and suggestions are always welcomed, please send them to alison@effectivenessevaluation.org.

Adherence: meaningful outcome or explanatory variable?

Lead investigator: Gene Colice, Washington Hospital Center, Wash., USA

Background: Treatment adherence can mediate outcomes, but it may also be a marker of disease severity and possible *predict* treatment outcome – the relationship is complex.

Aim: An observational study designed to investigate the bi-directional relationship between database markers of asthma treatment adherence (proxy measure: medication possession ratio [MPR]) and asthma control. Specifically:

- What is the impact of MPR (and change in MPR) on asthma outcomes?
- What is the impact of asthma outcomes on MPR (and on change in MPR)?

Status: Gene and Alison created a first protocol draft in collaboration with the study's working group. The working group have reviewed and helped to refine the protocol. Alex Dima has been working on the statistical methods section of the protocol and a final protocol should be ready for ADEPT (ethics) approval shortly.

Research team: Cynthia Rand (USA); Eric van Ganse (France); Iain Small (UK); Hilary Pinnock (UK); Alexandra Dima (Netherlands); Janet Holbrook (USA); Michelle Eakin (USA), Miguel Roman Rodriguez (Spain).

Oral steroid burden in refractory asthma

Lead investigator: Liam Heaney, Queens' University, Belfast, Northern Ireland

Background:

- Liam coordinates the British Thoracic Society's severe asthma registry in the UK – 1200 large dataset (with good phenotypic data) of patients with refractory asthma who are receiving oral steroids.
- Liam and colleagues have a paper in *Thorax* looking at the direct costs in the BTS registry.

- It often stated that asthma costs are driven by unscheduled healthcare resource utilisation, but the drug costs can significantly outstrip the cost of unscheduled healthcare use.
- There is a need to understand the true cost of refractory asthma if future high-cost drugs are to be justified.

Aim: Through REG the goal is to use a large UK primary care database to compare the steroid load in a refractory asthma population to that of (matched) a milder asthma population and non-asth-matic controls. The study will evaluate the comorbidity prevalence (stratified by age) and use those rates to work out the true cost of asthma in these patients.

Status: The protocol has been through an iterative revision process and has now been approved by ADEPT. Data extraction is underway.

Research team: Joan Sweeney and Chris Patterson, Queens' University Belfast, Northern Ireland.

Asthma risk prediction

Lead investigator: Mike Thomas, University of Southampton, Southampton, UK

Background:

- The planned study builds on asthma risk prediction work the charity AsthmaUK have been leading in the UK, and that Mike Thomas has been involved in.
- Asthma management has typically focussed on asthma control and its assessment rather than on a patient's exacerbation risk. Control is an important factor in asthma management, but there are independent factors that predict exacerbations, e.g.: comorbidities, smok-ing, adherence, exacerbations history.

- Patients are always told to take their medication and to be adher-ent, but if they are in a low risk group it could be entirely reason-able that they find a treatment strategy to cope with symptoms that is suitable to them.
- Risk strategies are used commonly in other diseases, but less so in asthma.

Aim: To look at patients' exacerbation frequency and construct (using regres-sion modelling) prediction tools that try to predict a patient's risk of future exacer-bations, by assigning them a "score" indica-tive of their level of risk. The tool will then be validated across different databases.

Status: Following a working group telecon, Mike and Alison created a first protocol draft which has since been reviewed by the group and refined via an iterative email process. The protocol is virtually agreed and now needs to be submitted to ADEPT for ethics approval. Discussions are beginning with the database and statistics teams.

Research team: Ian Pavord (UK); Alan Kaplan (Canada); Dirkje Postma (Neth-erlands); David Price (UK); Cindy Rand (USA) Gene Colice (USA); Todor Popov (Bulgaria); Janet Holbrook (USA); Hilary Pinnock (UK); Iain Small (UK); Emillio Pizzichini (Brazil), Vibeke Becker (Denmark).

Update on REG's Year 1 Research Activities (continued...)

Working with Medicare data: cost effectiveness of pulmonary rehab in COPD

Background:

- REG had hoped to collaborate with the COPDGene® Group to link the phenotypic data available in the COPDGene dataset (~10,000 COPD patients collected across 17 US sites) with Medicare claims data to explore the healthcare costs associated with different COPD phenotypes and in different COPD subgroups. Unfortunately, this collaboration does not look possible at this time.

- The cost of accessing Medicare is relatively low, so an alternative study working with Medicare data in COPD patients aged ≥65 years (i.e. those eligible for Medicare) has been devised.
- National Jewish Health (NJH), in Denver, Colorado, has a dataset of ~3000 COPD patients (of whom ~2000 are likely to be on Medicare).

Aim: To assess whether pulmonary rehab is cost-effective in COPD by linking the NJH data to equivalent Medicare claims.

Status: There is no protocol written at this stage. Input from REG collaborators is invited to help write a broader protocol that can be submitted to the NJH IRB for approval.

Ideas suggested during the meeting: Explore the effect of having _both asthma and COPD_ – there are unmet research needs in this area. Replicate the analysis in _other national datasets_. Possible UK datasets: Southampton/Hampshire (Mike Thomas); Glasgow (John Haughney); national COPD audit starting 2014 (Rupert Jones); Sally Singh.

COPD and blood eosinophils: predictive of future risk? (exploratory data)

Background:

- A recent study, led by David, showed a strong association between blood eosinophils and: (i) poor asthma control and (ii) more intense therapeutic management.
- Following a telecon with the REG COPD & Blood Eosinophil Study Working Group, some exploratory work has been carried out to get a feel for the data available for the study.
- Approximately two-thirds of COPD patients have blood eosinophil records. UK physicians are required (under the Quality and Outcomes Framework) to take blood counts for a number of conditions so blood count is presence of a record is not marker of more severity).

Aim:

An observational study to establish the relationship between blood eosinophil count and:
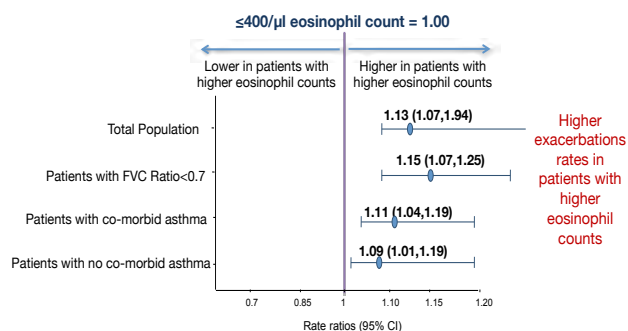
- Future COPD exacerbations.
- Response to COPD therapy; and
- Validate blood eosinophil count as an valid and repeatable endpoint in COPD

Lead investigator: David Price, University of Aberdeen, Aberdeen, UK

Research team: Alvar Agusti (Spain); Antonio Anzueto (USA); Ian Pavord (UK); Claus Vogelmeier (Germany); Nicolas Roche (France); Dirkje Postma (The Netherlands); Emillio Pizzichini (Brazil); Todor Popov (Bulgaria); Daryl Freeman (UK); Dermot Ryan (UK); Rupert Jones (UK); Alberto Papi (Italy).

Exploratory analysis approach: Eligible patients (n=~37,000) had an eosinophil count and at least one year of ("outcome") data after the date of the eosinophil count record for exacerbation evaluation. An exacerbation was defined as a hospitalisation for COPD or coded for a respiratory event, acute oral steroid use in conjuction with a respiratory review or antibiotics with evidence of a respiratory review.

Patients were categorised by eosinophil count ≤ 400μL (~90%) and > 400μL (~10%). This threshold was chosen because it was the threshold used in the asthma study, discussed above. The appropriate threshold for COPD will be explored in the full study.

Baseline description: There was no real difference in lung function severity between the ≤400μL and >400μL patient groups. Approximately 42% of patients with lower blood eosinophils had comorbid asthma vs 48% in the >400μL group. Patients with eosinophil count >400μL tended to be on slightly more medication and higher ICS doses.

These exploratory data suggest that patients with an eosinophil count >400 μL may have higher COPD exacerbation rates than those with eosinophil blood counts ≤400 μL. A fuller study is planned that will explore the appropriate eosinophil threshold and other issues raised in the meeting discussions.

Exacerbations: summary by subgroup

≤400/μl eosinophil count = 1.00

Lower in patients with higher eosinophil counts | Higher in patients with higher eosinophil counts

Subgroup	Rate ratio (95% CI)
Total Population	1.13 (1.07,1.94)
Patients with FVC Ratio<0.7	1.15 (1.07,1.25)
Patients with co-morbid asthma	1.11 (1.04,1.19)
Patients with no co-morbid asthma	1.09 (1.01,1.19)

Rate ratios (95% CI)

Higher exacerbations rates in patients with higher eosinophil counts

Exploratory findings: Overall the incidence rate of exacerbations was 13% higher in the group of patients with raised eosinophil counts (p<0.001). The rate was ~15% higher in the subgroup of patients with spirometry-defined COPD. The exacerbation rate remained significantly higher in patients with raised eosinophils even when patients with comorbid asthma were excluded (9% higher than for patients without raised blood eosinophils)

Discussions: points

- ICS is a negative confounder.
- Past work by Dirkje Postma et al has shown eosinophils can be raised by comorbidities. Exploring this possible link could be interesting.

- A Ghent study found the upper limit of normal in severe asthma patients to be 270mL (median 220mL).
- Medication posession ratio during the outcome period will be used to explore whether the raised eosinophil and exacerbation rates could be a marker of poor adherence.
- What is raised vs normal? The study will need to look at readings outside the "window" around an exacerbation. Total blood count could be used as a marker.
- Mona Bafadhel's study suggested eosinopenia could be a sign of sepsis.
- Interesting subgroups: ex smokers vs smokers; patients with no atopic history.

4

Update on REG's Year 1 Research Activities (continued...)

Nicotine replacement therapy and cardiovascular risk

Lead investigator: Gene Colice, Washington Hospital Center, Washington., USA

Research team: Annie Burden (UK); Richard Martin (USA); Alan Kaplan, (Canada); Joergen Vestbo (Denmark); Tarita Murray-Thomas (UK).

Background: Particularly with the advent of e-cigarettes there has been interested in whether there is any risk associated with nicotine replacement therapy (NRT). A grant application was approved by the UK's Medical Research Council to carry out a study exploring the potential cardiovascular (CV) risk of NRT compared to matched controls receiving smoking cessation advice only.

Top-line study summary: At an index date patients received either (i) smoking cessation advice (SCA) or (ii) NRT (no quit attempts were permitted over the prior baseline, characterisation year). NRT and SCA patients were matched 2:1 (~16,000 : ~33,000) on gender, age, hypertension diagnosis, CV diagnosis, diabetes, and COPD.

Headline finding: Patients prescribed NRT had significantly shorter times to first cerebrovascular disease diagnosis and all-cause morality than patients receiving SCA only.

Outcome period	Annual Cost
4 weeks after first NRT prescription / SCA	No significant differences
52 weeks after first NRT prescription / SCA	Significant differences in: • Time to cerebrovascular disease diagnosis • All-cause mortality survival times • Cerebrovascular & cardiovascular consultation rates
Ever after first NRT prescription / SCA	All-cause mortality survival times

Discussion: No concrete conclusions can be drawn, but it is hypothesis generating *it does suggest there is a signal worth exploring*.

Comments:
- There could be an undetected confounder that was the reason patients received NRT rather than SCA (although they were matched on baseline characteristics, inlcuding C).
- Secondary care consultations can be a predictor of mortality – it may be worth matching on (or at least looking at) secondary care resource utilisation over the baseline year.
- It is interesting that cerebrovascular diagnosis and consultations increase more than those for cardiovascular disease. The two conditions have different blood pressure profiles, with cerebrovascular disease perhaps more susceptible to the effect of by variations in blood pressure, which nicotine levels could drive.

Asthma endpoint validation study

Lead investigator: Richard Martin, National Jewish Health, Denver, Co, USA

Research team: David Price (UK); Alexandra Dima (Netherlands); Gene Colice (USA); Emilio Pizzichini (Brazil); Janet Holbrook (USA); Todor Popov (Bulgaria); Nikos Papadopoulos (Greece); Guy Brusselle (Belgium); Helen Reddel (Australia), Elliot Israel (USA); Alan Kaplan (Canada).

Background: Observational studies often face reviewer challenges, such as:
- Are the baseline and diagnostic data reliable and complete?
- Have all areas of potential bias been accounted for… or is there confounding by severity?
- Are endpoints valid when they differ from validated RCT tools, e.g. ACT, ACQ, etc?

Agreeing on gold standard outcome measures for asthma is still a research goal rather than a reality, both for RCTs and for real-life research – there is no perfect assessment. The best that can be done is to attempt to validate the existing tools against each other and try to understand the differences between them.

Aim: to validate a series of objective asthma control measures that have been used in published real-life research in terms of their:

- **Validity:** their clinical relevance, i.e. the extent to which they reflect the clinical reality of interest. Where possible they will be validated against RCT tools.
- **Responsiveness**: the extent to which they respond (where appropriate) to guideline-recommended treatment.
- **Predictiveness**: the extent to which the measure is associated with risk of future asthma exacerbations.
- **Reliability:** internal consistency.

Study design: The study draws on data from the Optimum Patient Care Research Database (OPCRD) because it not only contains patients' electronic medical records (primary care) but also (in a subset of patients) disease-specific questionnaire data, which enables objective database markers of asthma

Update on REG's Year 1 Research Activities (continued...)

Asthma endpoint validation study (continued)

control to be compared to patient reported outcomes (PROs).

To assess the **predictiveness** and **responsiveness** of the database markers of control, patients were characterised over a one-year period prior to an index date (at which point they either initiated ICS or stepped-up existing ICS dose). The effect of the treatment change was evaluated over the following one-year period (making suitable adjustments for baseline confounders).

To **validate** database outcomes against corresponding RCT tools /questionnaire data, patients were characterised over the one-year period prior to the date the questionnaire was issued. Database asthma control status was then compared to the questionnaire data / RCT asthma control tool status.

Eligible patients were aged 5–16 years, had ≥2 years of continuous practice data; an asthma diagnostic code ± questionnaire data. Patients were excluded if they had any other chronic respiratory disease diagnoses or were receiving maintenance oral steroids.

Endpoints to be evaluated: a number of database endpoints will be evaluated: "control"; exacerbations; SABA usage (as a proxy for symptoms); controller-to-reliever ratio; medication possession ratio; "treatment stability"; hospitalisations (inpatient admissions) and oral thrush (as a possible side-effect of treatment). The data presented at the ERS congress was the preliminary work that has been carried out on validation of database markers of control only – Risk Domain Asthma Control and Overall Control (see box for definitions).

Preliminary findings: RDAC and OAC were compared against GINA current control (i.e. against symptom assessment only, not against GINA's risk assessment). GINA current control was categorised as: totally controlled; partially controlled; uncontrolled.

Cross tabulations were produced and asymmetric tests (to see how RDAC and OAC compared with GINA current control; Somers D) and symmetric tests (to see how the two compare; Kendall's Tau B). Associations between RDAC / OAC and GINA were classified as small if they were ~0.1; medium if they were ~0.3 and strong if they were ≥0.5.

RDAC had only small associations with

> **Risk Domain Asthma Control (RDAC):** absence of the following aspects of asthma risk during the outcome period:
> • Asthma-related: A&E attendance; Hospitalisation (in-patient admission), or out-patient department attendance
> • GP consultations for lower respiratory tract infections (LRTIs)
> • Prescriptions for acute courses of oral steroids
> Uncontrolled = all others
> **Overall Control (OAC):** defined as:
> • Attainment of RDAC, and
> • Minimal impairment – average SABA daily dose of: **UK:** ≤200mcg salbutamol / ≤500mcg terbutaline; **USA:** ≤180mcg salbutamol / albuterol or ≤500mcg

GINA's current control (i.e. associations of 0.1–0.2). OAC had slightly stronger associations, ~0.3, but they were still only moderate (see table, bottom right).

The association between the disaggregated components of RDAC and OAC and GINA current total control status were also evaluated (using ordinal regression) and the three most predictive components in the multivartite analysis were: oral steroids; SABA usage and antibiotics coded for lower respiratory. SABA usage was the strongest predictor. When repeated as a binomial regression for GINA total+partial current control the results were very similar – overall *SABA usage is very predictive of GINA current (total ± partial) control.*

Appropriate OAC thresholds for SABA usage were also explored to see if they could be optimised. Optimum thresholds were identified by mapping OAC uncontrolled patients to GINA current uncontrolled patients to maximise the matches and by using ROC curve analysis. Using this method, the optimum thresholds were found to be:
• Full population: 110mcg
• Non smokers: 110mcg
• Current smokers: 180mcg
• Current + ex-smokers: 160mcg
When the earlier modeling was repeated using these new SABA thresholds in the OAC definition, the association between OAC and GINA current control strengthened.

Responsive: RDAC improve in response to guideline-recommended therapy (ICS initiation or step-up). However, OAC deteriorated in the outcome year (i.e. after ICS initiation or ICS step-up,

most likely as not all intiation patients were diagnosed and commenced on SABA at the start of their baseline year and also because SABA usage may increases with duration of disease. Thus: *SABA may be a good predictor of GINA current control status, but it is not a very responsive measure.*

Predictive: All the components of RDAC and OAC were evaluated to see which were most predictive of future exacerbation risk. For patients initiating therapy, asthma-related hospitalisations; asthma-related out patient department attendance; antibiotics coded for lower respiratory and oral steroids were most predictive of future risk (SABA usage was not). For patients stepping-up ICS therapy at the index date, hospitalisations were not predictive (most likely due to small numbers), but oral steroids, lower respiratory antibiotics and SABA *were* predictive.

Antibiotics coded for lower respiratory reasons have been included in database measures of control on the rationale that asthma exacerbations are often mis-diagnosed as lower respiratory tract infections. In both cohorts, this component was found to be predictive of future risk.

NB. These are preliminary data. A working group review meeting will be held when the analysis is complete.

Asthma control validation

Association thresholds: 0.1 small, 0.3 medium, 0.5 large

GINA Current Control	Risk Domain Asthma Control			Total
	Controlled		**Uncontrolled**	
Controlled n (%)	233 (12.6)	1224 (66.4)	48 (7.7)	281 (11.4)
Partly Controlled n (%)	991 (53.8)		269 (43.0)	1260 (51.1)
Uncontrolled n (%)	618 (33.6)		309 (49.4)	927 (37.6)
Total n (%)	1842 (100)		626 (100)	2468 (100)

GINA Control in 3 cats = Somers'd [0.170] & Kendall's Tau B [0.138]
GINA Control in 2 cats = Somers'd [0.158] & Kendall's Tau B [0.142]

GINA Current Control	Overall Asthma Control			Total
	Controlled		**Uncontrolled**	
Controlled n (%)	233 (19.0)	906 (74.0)	48 (3.9)	281 (11.4)
Partly Controlled n (%)	673 (54.9)		587 (47.2)	1260 (51.1)
Uncontrolled n (%)	319 (26.0)		608 (48.9)	927 (37.6)
Total n (%)	1225 (100)		1243 (100)	2468 (100)

GINA Control in 3 cats = Somers'd [0.297] & Kendall's Tau B [0.275]
GINA Control in 2 cats = Somers'd [0.229] & Kendall's Tau B [0.236]

REG Standards-related activities

Nicolas Roche spoke on behalf of the REG collaborators who have been working on **quality standards for real-life research** – work that Nicolas has been leading and to which he has devoted substantial time and effort.

He extended his thanks to the other REG collaborators who have been working with him – Alvar Agusti, Eric Bateman, Guy Brusselle, Elliot Israel, Jerry Krishnan, Richard Martin, Alberto Papi, Dirkje Postma, David Price, Cynthia Rand, Helen Reddel, Mike Thomas – for both their high quality and quantity of input and support.

So far, the group have produced two papers on quality standards to help guide the assessment of quality within real-life research and to help improving the quality and profile of the field among many stakeholders – researchers, members of guideline groups, policy makers, database designers, journal reviewers and editors, readers.

The original intention was to produce one paper that clearly outlined a set of standards for real-life research. However, discussions at REG collaborators' meeting at the ATS in May highlighted a need to first clarify what "real-life" means and to design a way that studies can be appropriately described to explain the extent to which they reflect different aspects of real-life clinical practice.

The ATS discussions led to the development of a framework on real-life research and a second paper on the standards for use in real-life research (the two papers discussed on this page are also discussed earlier in this report in the *Publications update*, see page 2).

Paper 1: framework

The objective of the framework is to aid in appropriate description and classification of research to enable the application of appropriate quality standard assessments to help to establish the value of a given study to a population (and clinical decision) of interest. Firstly, the clinical question of interest has to be described in terms of:
(i) the target population and
(ii) the healthcare setting.
A literature review then needs to be performed and the studies in the literature need to be placed in the framework. If it is necessary to describe the study in greater detail, the PRECIS wheel can be used. Based on their position within the 2D study population / ecology of care framework, the relevant quality assessment tools can be established and used to evaluate which studies should be incorporated into decision making, policy planning, guidelines, etc. The REG framework paper includes references to different published studies that fit within different spaces within the framework.

In short, the idea is to *have a simple two-axis means of describing a study and its relevance to a given population and clinical setting.*
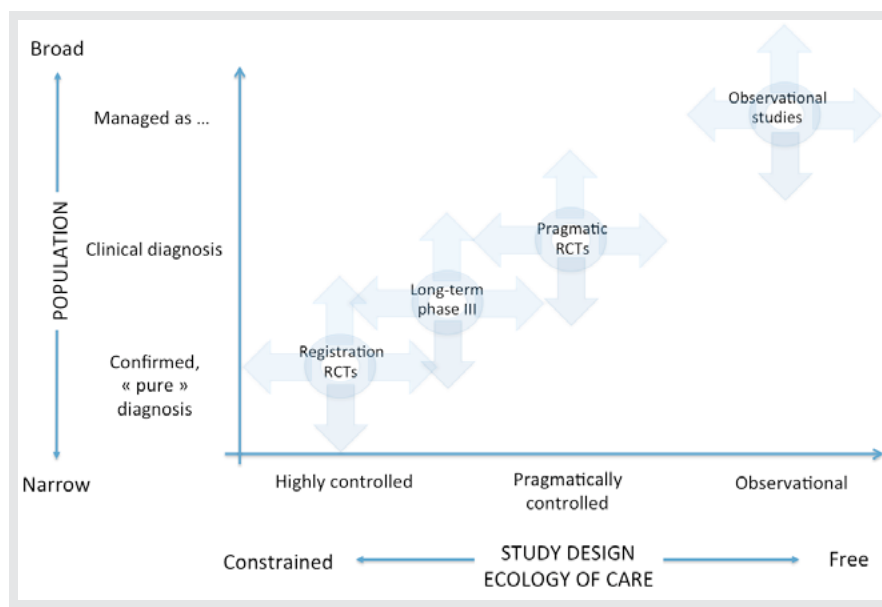
Paper 2: Standards

The second paper that the REG Standards Group have developed since the ATS Meeting in May is a paper for publication in the REG *ATSAnnals* supplement outlining standards for real-life studies. Although there is mention of pragmatic trials and reference to the extended consort statement, the paper focuses on standards for observational, database studies.

The paper builds on (and in many instances repeats) a review published ten years ago by REG collaborators David Price and Mike Thomas alongside co-author Jennifer Cleland in *Expert Opinion in Pharmacotherapy*, titled: *"*Database studies in asthma pharmacoeconomics: uses, limitations and quality markers (2003;4(3):1–8).

The *ATSAnnals* supplement paper on standards:

- Proposes a checklist of key quality markers that should helps with the development of protocols and should also help guideline developers and anyone attempting to appraise the available real-life literature. It does not produce a score, but details a number of qualitative features of a high quality / well described study protocol.
- Signposts other quality appraisal tools which should be applied as appropriate, e.g. CONSORT; SPIRIT; UNLOCK; STROBE; EMA-ENCePP.
- Offers recommendations for the:
  – Preparation
  – Analysis
  – Reporting
  of observational studies.

Standards-related discussions – should REG set up a taskforce?

Perform a critical appraisal of the evidence

IDEA: To conduct a critical appraisal of the existing "real-life" literature base in respiratory medicine. Indicate what studies are of sufficiently high quality to be worthy of consideration by guideline bodies and publish a consensus paper on how to critically appraise real-life data.

PROS:

- It would enable the utility of the study population / ecology of care framework to be tested.
- It would provide an important, critical review of the field. E.g. a real-life COPD study was published recently that failed to match patients on index date (year of treatment change). In David's past work this has proven to be a very important confounder because of the substantial evolution in COPD management approach that has occurred in recent years. Due to changes in management approach, patients with more recent index dates tend to look far more severe (receiving more therapy, receive more treatment changes, etc). Without a critical appraisal of the existing evidence and opportunity to highlight some of these important methodological issues, mistakes will continue to be made.

CONS:

- It would be a lot of work!
- We may lose friends... it might be necessary to annonymise it.

COMMENTS:

- Some sort of **scoring system** would need to be developed. The standards paper destined for *ATSAnnals* provides a checklist and guide for conducting and reviewing observational studies, but not a score. To be able to say: "these studies are 'in' and those are 'out'" requires a score.
- REG would need to **err on the side of critical** as it is a self-appointed group and could be discredited if it was seen to be lenient in its review of the evidence.
- This could be the objective of an REG Taskforce working through one (or more) of the major societies – ERS,

ATS, EACCI. The Taskforce could conduct a critical appraisal of real-life studies in asthma published within the last 5 years (for example). The findings and the evidence needs for different respiratory guidelines could be published as a Taskforce Report and then (drawing on the learnings of the review process) a Consensus Paper could be written on methods for appraising the real-life evidence

> *"One of the goals of REG is to get better integration of real-life data into guidelines ... for that we have to have high quality reviews and to move research and guidelines forward together – a taskforce would be helpful."*

base in respiratory medicine (ideally jointly badged by multiple societies).

– Comments from past ERS and joint ERS/ATS Taskforce members: Task-forces can be fairly unyielding and involve a substantial amount of hard work, writing and rewriting. The final output is a nice paper with substantial impact, but a lot of work has to go into it and the lead times can be long (up to 5 years).

– Comments from Jerry Krishnan (CER Co-Chair at the ATS) on the possibility of working with the ATS: The ATS is about to publish a research statement on comparative effectiveness research. The ATS have also been identifing delays in the time to publication of Taskforce documents (they are multifactorial). They want to achieve publication within a year of completion of the work to ensure it remains timely. What this field does not need is separate groups saying separate things, which could create confusion and suggest there is greater divergence of opinion than there truly is. A combined statement makes sense (although the process of combining different soicieties processes may become complex). The ATS's use of GRADE would not be a problem. GRADE is used for devising guidelines, the proposed paper sounds more like a "standards, concept paper" or a "perspective on data strategy" which would not require use of GRADE.

– Comments from Nikos Papadopolous (President of EACCI) and Leif Bjermer (Head of the EACCI Asthma Committee): There is a definite need for a follow-up to the Brussels declaration. EACCI is very open to the concept of effectiveness and would be happy to discuss taskforce opportunities with REG (David has been invited to talk to the EACCI taskforce committee at the end of September about the value of extending the evidence guideline base).

CONCLUSION: perhaps a task-force working through EACCI may be possible with the a view to partnering with other societies to produce a final consensus document...?

Other collaborations?

UNLOCK: REG and UNLOCK (the IPCRG group that has set minimum quality criteria for observational datasets) have agreed to work to support each others' joint goals. Niels Chavannes and Mike Thomas are members of UNLOCK and part of the REG Management Committee.

ENCePP: REG is recognised as a research network by the European Medical Authority's European Network of Centres for Pharmacoepidemiology and Pharmacovigilance). ENCePP provides a publicly accessible resource for the registration of pharmacoepidemiology and pharmacovigilance studies with a view to increasing transparency; reducing publication bias; promoting information exchange, and more. Although European-based, ENCePP's register is not limited to European studies only and will be used by REG at this time. REG may develop its own registry over time (if necessary), but would prefer to promote and utlise existing tools, were available.

Others? REG should look to forge links with STROBE and other quality standards bodies.

Thoughts on Integrating Real-Life Data into Guidelines

Eric Bateman had been invited to share his thoughts on how to begin the process of getting data from observational studies and pragmatic trials incorporated into guidelines.

Eric admitted that he had no experience of getting real-life data into guidelines and that it really depended on which guidelines were being targeted, and how they appraise the evidence. However he also reminded the group that GRADE does not completely disregards observational study data – it does not <u>disqualify it</u> – just requires it to be exceptionally strong evidence (see figure). The real challenge, therefore, is to establish a means of proving that an observational study can provide **"exceptionally strong evidence".** If the target guidelines are those of the ATS, and the ATS insist on using GRADE to appraise evidence, observational data will "squeak" to get in.

Eric went on to suggest that there has to be a willingness to set a standard which would be equivalent for studies that come from the observational design and that **the onus is on REG to set the standard and to live by that standard** in the hope of putting an end to the counterproductive "sniping" that currently exists.

Helen Reddel commented that one way to expand the scope of data available in a way that is, perhaps, less controversial than observational studies is to design studies that sit higher up the y-axis of the REG framework, i.e. that retain quite rigorous control, but broaden the study population. Eric agreed – the REG framework helps because it enables studies to be positioned and facilitates discussions about the applicability of the data, but that data from pragmatically designed trials would

be more readily acceptable to GRADE (and others) than being able to demonstrate the "exceptional strength" of observational study data. Eric finished the discussion by saying he would like those who demand GRADE-type analyses to take another look at what would be permissible – it is REG's job to trigger that process.

GRADING the quality of evidence and strength of recommendations Guyatt G, *et al*, *Chest* 2006;129:174-81

Grade of recommendation	Benefit vs Risk/ burdens	Method quality	Implications
1A strong recommendation, high quality evidence	Benefits far outweigh risks and burdens or *vice versa*	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B strong recommendation, moderate quality evidence	*ditto*	RCTs with important limitations or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C strong recommendation, low or very low quality evidence	*ditto*	Observational studies or case series	Strong recommendation, but may change when higher quality evidence becomes available

Setting up a Complex Interventions Working Group

Eric Bateman then spoke to the group about his hope to set up a Complex Interventions Working Group through REG.

Observational studies can real value by embedding management strategies in specific clinical scenarios (e.g. in the context of general practice in Britain, or wherever the data comes from). To be effective, interventions and management strategies have to be tailored to the specific context in which they are to be applied.

Observational studies and pragmatic trials can help evaluate interventions within certain health-systems to assess the impact and effectiveness of that intervention on the overall health system in which they are used. Few health systems (particularly those that are struggling financially) are naive when they look at data – they to understand not only the direct effect of an intervention, but also the implications on the rest of the health system and whether, for example, its use may

Proposed work-group

- **Title:** Utility cluster-randomised clinical trials to examine complex interventions to improve the quality of care offered to patients with chronic respiratory diseases
- **Purpose:** 1. To sensitize colleagues to validity of the research method, and its necessity address CRD in low/ lower-resourced countries
- 2. To sensitize health authorities to superiority of evidence from this source over audit alone (pre-post intervention)
- 3. To encourage use of complex interventions to address CRDs

require reorganisation of current clinics. Respiratory intereventions are complex interventions and they need to be studied as such at a complex level.

The "testbed" for Eric's past complex interventions work has lagely been in countries with under-resourced health systems: South Africa, Malawi, Botswana, Brazil and most recently Mexico City. In Malawi the combination of interventions included malaria, tuberculosis and and HIV. In South Africa (where malaria is less of a problem), the intervention analysis was adapted to include asthma, COPD, pneumonia and tuberculosis. The

work aims to blend the best elements of pragmatic studies with the best aspects of controlled trials and to measure the full spectrum of impact of the complex interventions.

Eric is looking for strategic partners to work with the Knowledge Translation Unit he has set up and hopes that REG (with the watchwords of "pragmatic" and "applicability") will be a natural home for this group and that some REG collaborators will find this work highly relevant and of interest.

The work is likely to take the form of **a literature review that will point out the strategic value of this type of research specifically for respiratory diseases**.

Eric closed by saying that asthma and COPD are among the chronic disease priority list, but treatment outcomes seem to be going backwards. Interventions must be studied in context in order to improve chronic disease management and to change governments views and health systems around the world.

Open Session : other real-life studies REG collaborators are involved

The 3CIA Initiative – Joan Soriano

Seventeen months ago, Joan told the group, the COPD world changed for good when GOLD published their new 3-dimensional categorisation of COPD (integrating lung function; symptoms and exacerbations).

There is now a need to understand the distribution of patients across the new GOLD categories and to understand the associated prognosis.

With this goal, the COPD Cohorts Collaborative International Assessment (3CIA) initiative was established. The **primary aim** of the initiative is to:

- Determine the distribution of the GOLD 2011 grading in well-defined, published, available COPD cohorts, and their prognostic validity up to 10 years (assessed in terms of COPD hospitalisations and time to death).
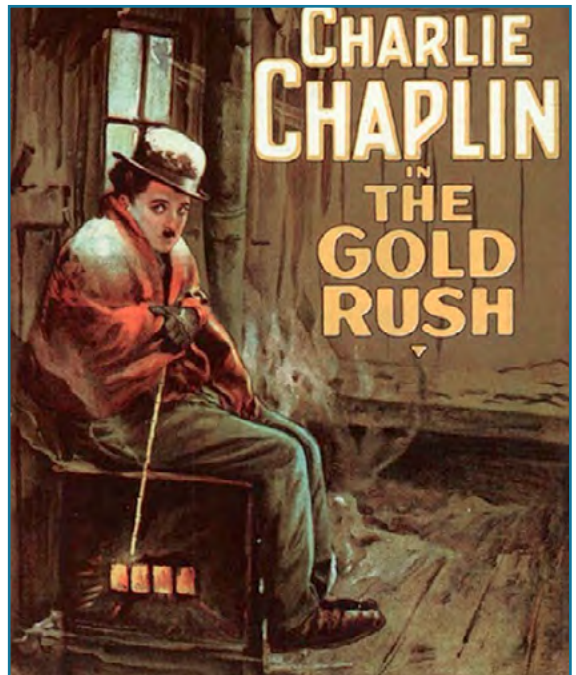
The **secondary aims** are to:

- Determine the primary objective by subgroups of COPD patients: by gender, age bands, smoking status, comorbidities, treatment,…
- Objectively quantify the thresholds of variables included in the current GOLD update proposal (lung function, exacerbations, mMRC, CAT, CCQ).

Status: Up to June 2013, the distribution of the new ABCD GOLD grades and their prognosis has been evaluated in 7 COPD cohorts. Pilot work suggest there is a variability in the distribution of categories in different COPD cohorts and also variability in the prognosis of mortality in these patients up to 10 years.

Study Design: a pooled retrospective longitudinal cohort study using cohorts provided by principal investigators of existing / published COPD cohort studies. 3CIA requestion blinded data with uniquie patient IDs. There are minimum dataset criteria that cohorts have to meet to be eligible. Participating cohorts include: COCOM-ICS and COPDGene.

**Objective of telling the REG collaborators about the 3CIA initiative:**

- To thank those who have already collaborated;
- To help convince others to collaborate
- To identify any REG collaborators who have COPD datasets and would be interested in participating in the initiative.

If you are interested in collaborating with Joan and the 3CIA group, contact Sofia Ramirez (3CIA liaison) at: asr.3cia@gmail.com

ASTRO-LAB – Eric van Ganse
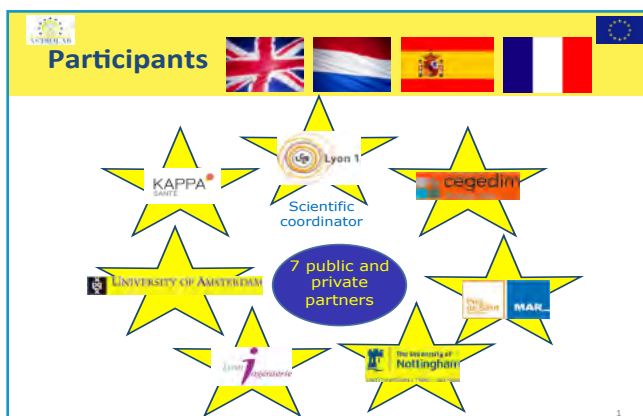
Eric van Ganse brought the meeting to a close by telling the group about the ASTRO-LAB initiative that he is coordinating (from Lyon) and that is being funded under the European Community's (EC's) 7th framework.

Background: The study grew out of the fact that the European Medicines Authority (EMA) set up a new organisation (ENCePP) that is committed to conducting pharmacovigilence and pharmacoepidemiology studies using databases. They requested proposals for a study to look at the safety of long-acting inhaled agonists in asthma.

The study Eric and his colleagues designed focussed on LABA adherence rather than potential LABA toxicities.

Study design: The ASTRO-LAB has been designed as a prospective cohort study that will link GPs database, national claims databases and patient reported data.

Eligible patients must be receiving LABA or ICS/LABA asthma therapy. Data (exacerbation and adherence data) will be collected over a two-year outcome period. The safety of LABAs will also be explored by estimating the rate ratio and rate difference of serious events in children, adults, and possible at-risk subgroups comparing exposure to LABAs alone and in combination with ICS to those in patients receiving ICS alone. The study will capture very detailed data on adherence via three sources: (i) so physician prescriptions; (ii) dispensing and resource utilisation records; and (iii)questionnaire data (currently in development). Monthly text messages and 4-monthly meetings will be used to help maximum data collection.

Although the study is being coordinated from Lyon, it involves collaborators from France, the UK (Nottingham), the Netherlands (Amsterdam). The goal is to build a 3000-strong patient cohort, half adults, half children. So far ~300 patients have been recruited in France and the first patients were recruited in the UK at the start of September. It will run for another 2 years.