

REG NEWS: AUTUMN UPDATES

REG at the ERS: highlights from Munich...



The 2014 ERS was a very busy, but hugely exciting time for REG. Our research was presented in the poster halls and oral abstract sessions, and our vision and thinking about the value and role of real-life research was shared with ERS delegates at the REG/UNLOCK symposium: *The Evolving Role of Real-Life Research in Respiratory Medicine* (see Box 1 for session & poster details).

It is through disseminating REG's work and ethos at these sort of international events that our efforts will start to delivery the impact we all hope.

Around the congress, we also held a collaborators' and supporters' meeting, where the business and strategy of the initiative was discussed (see page 2 for further details), and a research meeting to explore opportunities for REG in the areas of COPD eosinophil, and Asthma COPD Overlap Syndrome (ACOS) research.

We would like to extend a huge note of thanks to our ERS presenters, as well as to all who worked tirelessly behind the scenes to push our studies forward and to develop and review the (many and varied!) ERS materials.

The REG/UNLOCK symposium

was a significant milestone for real-life research. It was among the first times a session focussing on the role of real-life research has made it into the main body of the ERS's scientific programme. Despite a brief moment of panic when we learned that our opening speaker, was unable to make it, the session was both well attended and very well received. Enormous thanks go to our session chairs—Nicolas Roche and Guy Brusselle—who stepped into the breach, giving an unrehearsed, but excellent first presentation on *Real-life studies – a poor relation or important partner to the respiratory RCT*. Guy and Nicolas' very fresh and unique start to the session, was not only testament to their true professionalism, but also a beautiful illustration of how strongly held and fundamental the presentation topic is to REG and all REG collaborators.

The following presentations built on this great foundation, delivering a coherent and thought-provoking narrative about the potential role and value of (well-designed and executed) real-life studies.

Calling on data from published studies, David Price illustrated how real-life research can provide evidence for patient subgroups often excluded from RCTs and he emphasised that the choice of study design (real-life or interventional) is predicated by the research question being asked.

Niels Chavannes then spoke about the quality standards work being carried out by the REG/EAACI taskforce and our work around the development of

SYMPOSIUM

Chairs: Nicolas Roche & Guy Brusselle

- Real-life studies – a poor relation or important partner to the respiratory RCT

Presenter: *Christian J. Virchow (official); Guy Brusselle & Nicolas Roche (actual)*

- The implications of real-life (comorbid conditions, inhaler technique and lifestyle factors) on asthma management: is there any evidence available?

Presenter: *David Price*

- Developing and applying datasets and standards for high-quality real-life research; **Presenter:** *Niels Chavannes*
- Phase IV implementation studies: the forgotten finale to the MRC framework:

Presenter: *Hilary Pinnock*

ABSTRACTS

REG Endpoint Validation Study:

- Do SABA prescribing records reliably reflect patient-reported outcomes? *Richard J Martin*
- Do database asthma control measures predict future risk? *Guy Brusselle*
- Association between database and patient-reported exacerbations; *Richard J Martin*

Paediatric Asthma Step-Up

- Comparative effectiveness of Bpaediatric asthma step-up options: increasing ICS dose vs adding separate LABA; *Clare Murray*
- Paediatric asthma: pharmacological & non-pharmacological management; *Clare Murray*

COPD Eosinophil Study

- Blood eosinophilia and number of exacerbations in COPD patients; *Marjan Kerckhof*

BOX 1. REG events and presentations at the 2014 ERS - a busy time!

quality assessment tools and checklists that can be used to guide researchers, reviewers, journal editors, clinicians and guideline bodies in designing and appraising real-life studies and the implications of their findings. Hilary Pinnock then concluded the session with an interesting discussion of the role of real-life studies as implementation studies.

We also had six abstracts presented at the congress – two as oral presentations and four as thematic poster presentations. These abstracts were selected highlights from REG's on-going asthma endpoint validation; paediatric asthma step-up and

COPD & blood eosinophil studies, all of which are now approaching completion. We hope these "tasters" will have whet everyone's appetites for the final papers when they follow in 2015.



ERS poster hall: Richard Martin presenting some initial findings of REG's asthma endpoint validation work

MEETING UPDATES

REG Collaborators' & Supporters' Meetings at the ERS

REG COLLABORATORS' & SUPPOTERS' MEETING AGENDA

Tuesday 9 September 2014; Internationales Congress Center Munchen (ICM) Munich, Germany, Room 2.250

Time	Topic	Presenter
07:00 – 07:05	Welcome	David Price, REG Chairman
07:05 – 07:20	Constitution document	Thao Le, REG Director
	Organisational structure	
07:20 – 07:45	Research updates	Annie Burden; Marjan Kerkhof; Steve Turner; Liam Heaney; Andrew Wilson [See p3]
07:35 – 07:50	Research Ideas Pinboard Review	Eliot Israel [See p4]
07:50 – 08:00	EAACI Task Force update	Nicolas Roche [See p6]
08:00 – 08:10	APSR Congress 2014	Thao Le [See p6]
08:10 – 08:15	Publication News	David Price [See p5]
08:15 – 08:20	REG Summit 2015	Thao Le [See p5]
08:20 – 08:25	Other comments / discussions	All
08:25 – 08:30	Closing	David Price

REG's "official business" was carried out at a breakfast meeting at the conference centre on the Tuesday of the ERS. It was an opportunity for an update on progress with the formalisation and finalisation of REG's Constitution; to announce and changes to the organisational structure and to review the current status of on-going and future REG activities.

The organisational updates are summarised below; REG activity updates (studies, publications, taskforce, etc) follow on pages 3–6, summarising not only what was discussed at the ERS, but also any subsequent updates.

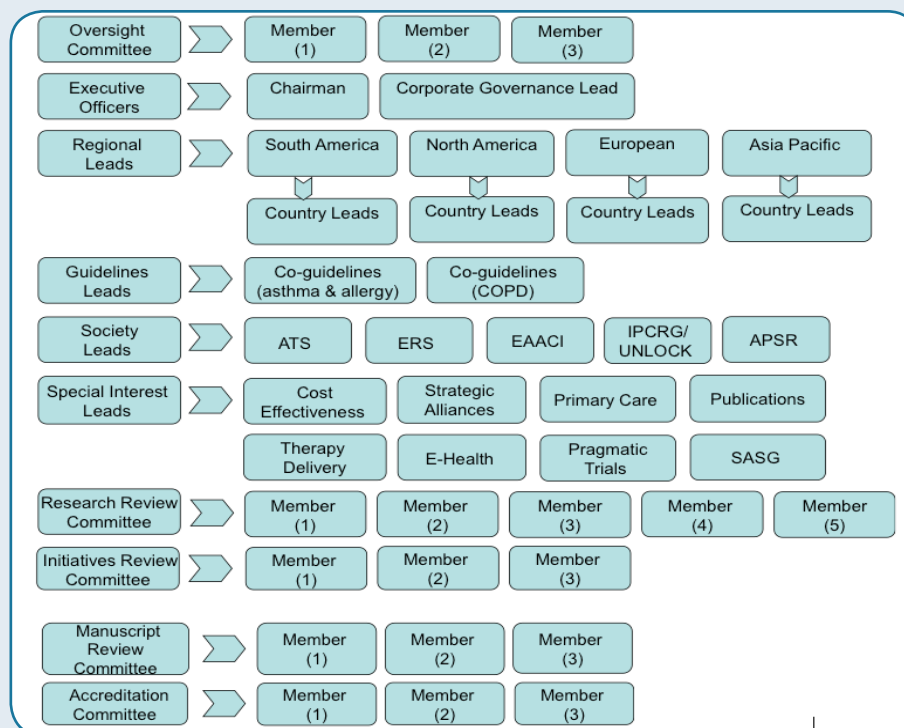
Constitution & Structure

Work has continued to develop a formal Constitution for the organisation – desired to ensure effective and efficient operations and attainment of REG's goals, and required to demonstrate transparency to members, supporters and the outside world.

The REG Council will now include: an objective **Oversight Committee** (to ensure the ethical, transparent and appropriate operations of the group); an **Executive Committee** (Chairman, Secretary and Corporate Governance Lead); **Regional Leads** (North America; South America; Europe and Asia-Pacific); **Guideline Leads** (Asthma and COPD); **Society Liaison Leads** (ERS, IPCRG, ATS, EAACI, APSR); **Special Interest Leads** (Cost-effectiveness; Strategic Alliances; Therapy Delivery; E-Health; Pragmatic Research; Primary Care; Publications; Small Airways) and a number of **Operational Committees** (Research Review Committee; Initiative Review Committee; Publications Review Committee; Accreditation Committee).

The rationale for this structure is to ensure representation, and promote participation, of collaborators from different geographical regions and areas of specialism within REG. It also ensures a wide, equitable and hopefully sustainable spread of roles and responsibilities.

From an research and publications perspective, there will also be a number of defined REG working groups (or study groups). The focus of these groups be an area where real-life research has the



potential to enhance, or "plug a gap" in the randomized controlled trial (RCT) evidence base. One such group will be the Small Airways Study Group (SASG), a steering group set up >5 years ago to evaluate the role of small airways management in obstructive lung disease utilising real-life methods. Other Study Groups identified so far include: **Adherence** (Lead: Gene Colice); **COPD Stability** (Lead: Marc Miravittles); **Validation & Standardisation of Coding** (Lead: Mike Thomas); **Database Resource Group** (Lead: Katia Verhamme); **Non-pharmacological Interventions** (Lead: Anne Bruton); **Child Health Group**

(Lead: Steve Turner); **ACOS** (Lead: Jerry Krishnan); **Cost Effectiveness** (Lead: Jon Campbell). If you have additional Study Group and/or Council Special Interest Lead suggestions or member nominations, please send them to Thao Le (thaole@effectivenessevaluation.org).

Collaborator Status Changes

REG collaborator Gene Colice announced his new role as lead physician on anti-IL13 programme at AstraZeneca. Gene has played a tremendous role as lead investigator on the REG adherence study and it was agreed that Gene will continue to lead REG adherence activities as an Associate Member of REG.

RESEARCH UPDATES

On-going Study Updates... Where are we now?

Asthma Endpoint Validation

Study description: led by Richard Martin, this study is a first attempt to compare a number of database (DB) endpoints used in published observational asthma studies to patient reported (PR) and RCT outcomes.

Key findings presented at the ERS:

- Small association between annual DB-recorded & annualised PR SABA use;
- DB-recorded SABA use is predictive of GINA Current Control Status;
- DB-recorded asthma control endpoints & PR endpoint (GINA current control) are all predictive of future exacerbation risk.

Status Summary:

- 3 poster presentations at the ERS.
- REG funding is being sought for a manuscript looking at the predictive power of DB-defined endpoints.

Asthma Risk Prediction

Study description: led by Mike Thomas, this study aims to better understanding which individual patient characteristics (Phase I) and combinations of characteristics (Phase II) are associated with increased future asthma exacerbation risk and, in so doing, to develop risk scoring tools to evaluate individual patient risk.

Phase I findings (stepwise reduced multivariable model): Patients with blood eosinophil count $>400/\mu\text{l}$ (vs. $\leq 400/\mu\text{l}$) had significantly increased odds of 2 or more exacerbations (OR 1.48; 95% CI 1.39–1.58).

Status:

- Phase I: paper in preparation for JACI
- Phase II: to commence Autumn 2014.

Paediatric Step-Up

Study description: led by Steve Turner, this study aims to use an observational paediatric dataset to explore the:

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

Status Summary:

- Analyses was completed in May 2014 and an oral abstract was presented at the REG summit
- 1xoral & 1xposter presented at the ERS
- Manuscript on predictors of step-up options written by Steve Turner and submitted to *Archives of Disease in Childhood* in September 2014.
- Additional manuscripts under discussion.

Adherence

Study description: Led by Gene Colice (with substantial collaboration from Alex Dima on the analysis), this longitudinal study aims to explore the bidirectional relationship between asthma adherence and outcomes, i.e... Do high levels of adherence result in well-controlled disease, or do they reflect poorly controlled patients with high medication dependency?

Status:

- Data extraction completed in February
- Study methodology presented at the REG Summit.
- Optimum adherence "measure" has been tested within the dataset
- Longitudinal, interaction analyses are now under way.

COPD Risk Prediction

Study description: proposed and led by Daryl Freeman, this study aims to identify routinely collected patient characteristics that may be associated with an increased risk of future COPD exacerbations.

Status:

- Analysis used COPD blood eosinophil study dataset (as detailed above).
- Results were presented at the REG summit in June.
- Manuscript planning and preparation is now under discussion.

COPD and blood eosinophils

Study description: led by David Price, this study aims to evaluate the relationship between "steady state" blood eosinophil count and COPD exacerbations (Phase I). It also aims to "validate" blood eosinophils as a reliable, responsive and meaningful measure.

Key Phase I finding:

- Blood eosinophilia ($\geq 450/\mu\text{l}$) is associated with higher COPD exacerbation rates in non-smoking patients treated with ICS.

Status:

- The analysis is now complete.
- Oral abstracts were presented at the REG summit and at the ERS congress.
- Manuscript proposal currently in development.



Refractory Asthma

Study description: led by Liam Heaney (and conducted by his research team at Queen's University Belfast), this study aims to evaluate the healthcare costs associated with comorbidities of refractory asthma and systemic steroid exposure. Using a UK observational database, the findings will be compared to those from an analysis of the BTS severe asthma registry.

Status Summary:

- An abstract of the preliminary analysis was presented at the REG Summit in June 2014
- The per protocol analysis is on-going.
- There is substantial interest from REG supporters in this study and possible future avenues for funding subsequent/follow on analyses.

COMING UP...

REG Research PinBoard: 2014 short-listed studies



The REG Research Pinboard was set up to give all collaborators and supporters the opportunity to propose research ideas – research questions that would be best answered through real-life methodologies. All submitted ideas are considered by REG's Research Review Committee and short-listed for REG research funding - REG's 2014 "Top Ten" are summarised below. The submission, review and selection of research ideas will take place annually to ensure research topics remain up-to-date and relevant to the field.

NUMBER	PROPOSED BY	STUDY IDEA
1	Grigg J	Asthma Management in the under 5s
2	Murray C, Papadopoulos N	Is the addition of oral antibiotics with oral corticosteroids in an acute asthma exacerbation of benefit in terms of time to next unscheduled GP visit with asthma; time to next oral corticosteroid prescription and use of SABA of the following 6 months? Is any effect seen antibiotic class specific?
3 (joint)	Lisspers K, Chavannes N, Kocks J, et al	UNLOCK study: are pharmacological RCTs relevant to real-life asthma populations?
	Kern E, Martin R	Outpatient factors predictive of emergency department use and hospitalizations among patients with COPD
5	Turner S	Are Patient Characteristics Predictive of Response to Step Up Treatment in Children with Asthma?
6 (joint)	Monteagudo M, Miravites M	Incidence of Cardiovascular Disease in Newly Diagnosed COPD Patients in Primary Care
	Stallberg B, et al	UNLOCK Study: the prevalence of comorbidities in COPD patients and their impact on the quality of life and COPD symptoms in primary care patients
	Williams S	Developing a validated claims-based algorithm for severe COPD
	Kern E, Martin RJ	Using Medicare Claims Data to Determine the Effect of Pulmonary Rehabilitation and CT Phenotypes on the Occurrence and Cost of Severe Exacerbations of COPD
10 (joint)	Ryan D, Pinnock H, Jon P	Development, Validation and Evaluation of a Short form of EXACT (Exacerbations of Chronic Pulmonary Disease Tool) Questionnaire for Clinical Use and Self-(tele) Monitoring
	Budmann S, Buhl, R, Syk J, et al	Evaluation of fractional exhaled nitric oxide for predicting response to inhaled corticosteroids for patients with non-specific respiratory symptoms
	Price D, Gopalan G, Shah T, et al	A New Methodology for Assessing Masery and Maintenance of Dry Powder Inhaler Technique in Adults with Asthma

What does being short-listed mean?

"Short-listed" studies are those that the REG Research and Reviews Committee have deemed to be most aligned with the research goals of REG and to be of highest priority for funding. These will typically be studies that address specific "gaps" in the existing evidence base; gaps that real-life research methods (be they pragmatic or observational) are most appropriate to address, i.e. not research questions that could be feasibly and more appropriately addressed through an RCT.

If my idea is short-listed, will it be funded?

Once REG has short-listed a study, it has committed to trying to secure some source of funding for it. The nature of the support (i.e. type of research grant) that REG secures will dictate how it is classified, i.e.:

- REG Studies:** where supporters fund REG to conduct the study with a (hands-off) research grant.
- REG Collaborations:** studies that are not product-specific/non-commercial, but that are funded by one REG supporter.

3. A Commercial Research Study:

a product-specific / commercial study funded by ≥ 1 REG supporter. Due to their commercial nature, these studies will no longer be carried out under the REG "banner". Instead they will be handled outside REG activities through direct supporter / collaborator communication. REG's role will be one of "match-maker" - matching the idea to an appropriate source of support. REG's goal is to find some form of support (whether 1, 2 or 3) for all short-listed study ideas.

COMING UP...

Upcoming REG Summit: Rotterdam 23–24 January, 2015

Our next Summit will be held in Rotterdam on the January 23rd–24th January (Hilton Hotel, Weena 10, 3012 CM) – do come and join us!

The theme for the summit—**Data-bases and Registries Around The World - Maximising The Yield**—will be a great opportunity to look beyond the databases that REG has used so far and to consider opportunities to collaborate at scale with other real-life resources around the world.

In addition to the main scientific sessions, there will be a number of Study Group meetings on the 22nd of January. These meeting will be an opportunity for REG's new Study Groups (see summary on p2) to formalise their remit and to plan their initial research, educational and publication activities.

As per the 2014 Summit, the programme will include plenary



Join us in Rotterdam in January for the 2015 REG Summit!

and educational sessions and workshops as well as a number of thematic research sessions - a great opportunity to present and share the real-life research you and your colleagues are carrying out, within REG and also within

your wider roles. Abstract submission is officially closed, but **last-minute abstracts are still being accepted**. If you have an abstract / some data to share, please send it to Vanessa Cattermole at: vanessa@effectivenessevaluation.org.

Publication news...!

2014 REG Summit Abstracts

The abstracts from our June Summit have now been published in *Primary Care Respiratory Medicine* (PCRM) and can be accessed online at: <http://www.nature.com/public/article-assets/npg/npjpcrm/abstracts/npjpcrm201473.pdf>

Thank you to the abstract authors and to REG's Paula & Vanessa for working with the journal to publish these in such a timely fashion.

RCCM Editorial: Database research

REG collaborators Rupert Jones and Alan Kaplan have recently published an excellent editorial in the Blue Journal entitled *Can Database Studies be used to make Tough Research Decisions?* (AJRCCM, 2014; 190(9):967-968). The editorial is a very interesting comment on Prieto-Centurion et al's study (in the same issue) which compares and contrasts database, insurance and RCT definitions of COPD.

REG Staff & Staffing Changes...

REG has dedicated staff who are always happy to hear from you, be it nominations for council members, suggestions and recommendations for the group, or to address any queries you may have. To help best direct your questions / comments, here's a brief "back-office" summary:

- **REG Director – Thao Le:** thaole@effectivenessevaluation.org
- **REG Research Lead – Vanessa Cattermole:** vanessa@effectivenessevaluation.org
- **REG Administration Coordinator – Emily Leinster:** emily@effectivenessevaluation.org

Please note: Paula Brown is no longer with REG, but we extend our warm thanks to Paula for all her great work over the last 6 months. We also want to **welcome back Alison Chisholm**, who'll be working on a freelance basis to support REG from a communications and publications perspective, it's great to see her involved again: alison@effectivenessevaluation.org.

Webinars

To provide a dynamic and timely forum for presenting, discussing and seeking peer advice on real-life research activities, REG will be launching a programme of Research Webinars in November this year. The first webinar will be held on Friday the 27th of November, 1–2pm (GMT; London time). The format will be 15-minute research presentations, followed by 15 minutes Q&A to allow a full, interactive discussions. We really do urge you to support this newest REG initiative so that we continue to be a dynamic and interactive organisation that enables rapid peer review and the sharing of best practice.

Vanessa has/will circulate "calls for presentations" ahead of time. You will also receive an invitation to join each event via the Webinar software is **JOIN.ME**. Simply click the link in the email to join and view the presentations. To hear the audio via your computer you'll have to download the desktop App (a 1-click process). Alternatively you dial into the audio via a landline/mobile while viewing the materials online. If in doubt, please contact Vanessa Cattermole.

Current & Future Activities...

REG / EAACI Quality Taskforce Progress

The REG taskforce was set up in recognition that there is a lack of clear guidance on how to appraise non-RCT evidence – what constitutes quality in terms of design and delivery; how to interpret the data; and so on. 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. So... If REG wants to see valuable, high-quality real-life research being appropriately incorporated into guidelines, we have to help provide the tools and the methodologies necessary to 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. EAACI share this view and have supported our proposal for a taskforce that will conduct a critical

review of the existing real-life asthma evidence base, identifying high-quality real-life studies whose results may be worth integrating into clinical guidelines.

Progress to date

A review of the literature on asthma comparative effectiveness research (CER) from 2004/09 has been carried out, identifying 1,400 articles. PICOT questions have been proposed by REG collaborators, the top 3 of which (as voted by the collaborators) will be used to further narrow the search.

Development of a quality assessment tool has begun, led by Jon Campbell. Existing quality assessment tools have been reviewed and combined to develop a CER REG quality-assessment “wheel” (inspired by the PRECIS wheel). Once finalised, the tool will be applied to the results of the focussed literature review and the findings published and presented at the 2015 EAACI congress.

Horizon 2020

Horizon 2020 takes over from EU FP7 as the source of European Union research, technology and innovation grants, up to and including 2020.

Horizon 2020 seeks to support the production of high-quality outputs (products and/or devices) and innovative ideas that with the potential for job creation, with a view to stimulating the EU economy and wealth creation. Successful funding bids will also bring together academic and commercial partners and will develop effective and efficient interdisciplinary collaborations.

On behalf of REG, David Price has accepted an invitation, to participate in the next Horizon2020 call for proposals *Establishing effectiveness of health care interventions in the paediatric population*. The proposal is confidential at this stage, but more news and updates will be featured in future REG newsletter issues.

Future Congress Events: 2014/15

ASPR 2014

November will underline REG's global reach with its first formal Asia-Pacific Events – a symposium at the Asia Pacific Society of Respiriography (ASPR) Annual Congress in Bali. The symposium will be similar in format to our ERS symposium (recognising the differing geographical profiles of the APSR and the ERS), with the title: *The Evolving Role of Real Life Research in Respiratory Medicine* and presentation titles: (i) Real-life studies – a poor relation or important partner to the respiratory RCT?

(ii) The implications of real-life on asthma management: is there any evidence available?

(iii) Leveraging datasets and insisting on quality.

There will also be an REG collaborators/supporters meeting at the ASPR congress – to be held on Saturday 15 November from 9.30-11.30am (Bali local time). REG representatives will be discussing and promoting REG's activities and asking ASPR delegates to share their research experience and database resources in the hope of further growing our list of Asia-Pacific collaborators.

EAACI 2015: Symposia

REG has had two symposia accepted for the 2015 EAACI congress in June.

The first considers the role of database studies in exploring complex allergic airways disease: *Harnessing primary care databases to unpick the complexities of allergic obstructive airway disease*. Presentations (given by REG collaborators Niels Chavannes, Osman Yusuf and Ian Pavord, respectively) will focus on practical aspects of database research; unmet allergy and rhinitis research needs, as identified from database studies, and the potential use of databases in allergic obstructive airways disease. The second symposium will report the findings of the REG/EAACI taskforce, activities, titled: *From efficacy-*

based to effectiveness-based guidelines in asthma: a paradigm shift? It will include presentations from the REG Taskforce Lead, Nicolas Roche, on the studies identified from by the taskforce as contributors of quality data to the existing CER asthma evidence base. David Price will then look at remaining gaps in the evidence base, and identify future research targets for asthma CER. The final presentation will compare and contrast “real-life” and database definitions of asthma studies with a view to helping guideline developers understand the “applicability” of study findings.

Our thanks go to Dermot Ryan and Nikos Papadopolous for their review of the session proposals and to Dermot for championing them at the planning session in February this year.

ATS 2015: Symposium

Thanks and congratulations to REG collaborators Jerry Krishnan and Barry Make for their successful ATS session proposal: *High Profile Effectiveness and Efficacy Research with Conflicting Results - Which to Believe*. The session, for next year's ATS congress in Denver, picks up on the challenge of what to do when real-life/effectiveness

studies return results that appear to conflict with RCT/efficacy findings. This issue was noted in the ATS's Comparative Effectiveness Research Statement and is a real obstacle to the acceptance and utility of effectiveness study results.

It promises to be a very interesting and important session.