Should evidence be obtained by RCTs only?

The role of RCTs and real life studies for better decision in respiratory medicine.

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on behalf of G. Caramori, R. Bodini, P.A. Santus

Conflict of interest disclosure

- ❑ I have no, real or perceived, direct or indirect conflicts of interest that relate to this presentation.
- X I have the following, real or perceived direct or indirect conflicts of interest that relate to this presentation:

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Grants/research support (to myself, my institution or department):	
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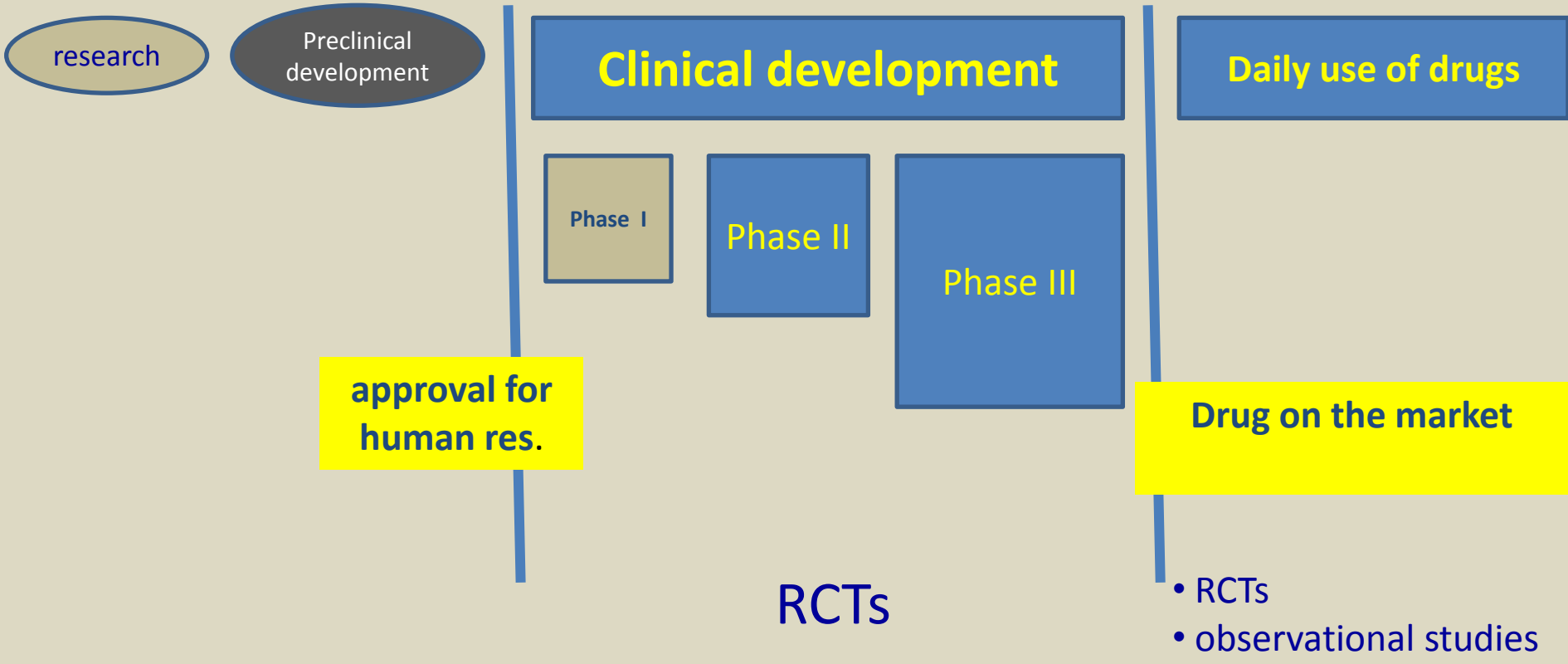
Research evolves by answering new questions, including questions on how research itself should be conducted.

Saturni et al, 2014



From Caputi A.P., Farmacologia, Minerva Medica, 2011, modified

Description of Levels of Evidence

Evidence Category	Sources of Evidence
A	Randomized controlled trials (RCTs). Rich body of data
B	Randomized controlled trials (RCTs). Limited body of data
C	Nonrandomized trials Observational studies
D	Panel consensus judgment

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Randomized clinical trials are considered the **most evident** source of data.

Observational studies have a **lower** level of evidence

Evaluating the Evidence
Is There a Rigid Hierarchy?

P. Michael Ho, MD, PhD; Pamela N. Peterson, MD, MSPH; Frederick A. Masoudi, MD, MSPH

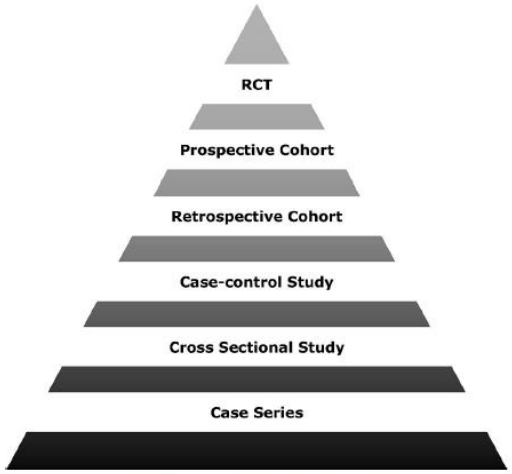

Figure. The pyramid of evidence.

(*Circulation*. 2008;118:1675-1684.)

Global Strategy for Asthma Management & Prevention 2015

Evidence category	Sources of evidence
A	▪ Well-designed RCTs or meta-analyses ▪ Consistent pattern of findings in the population for which the recommendation is made ▪ Substantial numbers of large studies
B	▪ Limited number of patients, *post hoc* or sub-group analyses of RCTs or meta-analyses ▪ Few RCTs, or small in size, or differing population, or results somewhat inconsistent
C	▪ Uncontrolled or non-randomized studies ▪ Observational studies
D	▪ Panel consensus based on clinical experience or knowledge

Editorial Comment

Respiration

Respiration 2014;87:9–10
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What We Talk about When We Talk about Randomized Controlled Trials

Alfredo Chetta Dario Olivieri

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What Proportion of Chronic Obstructive Pulmonary Disease Outpatients Is Eligible for Inclusion in Randomized Clinical Trials?

Nicola Scichilone Marco Basile Salvatore Battaglia Vincenzo Bellia

Respiration 2014;87:11–17

exsmoker with a smoke burden <10 pack-years were considered as selection criteria of asthmatic patients to a RCT. The authors found that only 5.4% of their asthmatic patients met these criteria. They applied the same procedure to the group of COPD patients and a FEV_1 <70% of predicted value, a significant smoking history (>15 pack-years) and absence of atopy were the selection criteria they considered. Only 17% of the COPD patients were eligible for the RCT. In line with these results, Travers et al. [4] found that in a group of 55 COPD patients undergoing treatment and identified by postal questionnaire and functional assessment, only a negligible percentage met the eligibility criteria of 18 RCTs cited in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.

Interestingly, the majority of asthma trials do not accept current/former smokers, while the majority of COPD trials exclude asthmatics, so there are no data on the large subgroup of patients (~30%) who have poor lung function and unfavorable clinical outcomes (e.g. frequent hospitalizations) [29,40–43].

Elderly asthmatic patients are another group traditionally excluded from RCTs, even though this clinically relevant population experiences high rates of hospitalization and asthma related death [29,44,45]. Excluding such patients and, for example those with comorbidities, results in a lack of treatment solutions in exactly the groups where they could have high clinical impact [29,46].

Pulmonary Pharmacology & Therapeutics 27 (2014) 129–138

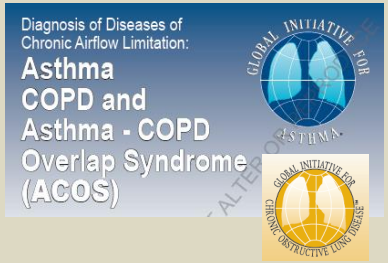


Table 1
Advantages and disadvantages of RCTs

	RCTs
Advantages	• Rigorous experimental design • Randomization • Blinding • Control • Rigorous analysis methods
Disadvantages	• Selected patients • Setting and monitoring bias • Economical limitations • Logistical and ethical restrictions • Unsuitable for complex treatments studies • Inappropriate for thorough evaluation of side effects • Short duration

On the other side, strict selection might focus only on patients who will respond better to the tested treatment leading to overestimation of treatment effects [53]. Patients included in RCTs are usually adept at inhalation techniques: they are instructed on the use of inhalers and frequently monitored. Adherence to treatment is usually high in RCTs as this is a prerequisite for randomization, assessed during run-in: a sort of pre-selection of the population that can maximize treatment effects [14]. Clearly, this does not reflect everyday clinical practice, largely characterized by poor inhaler technique and low treatment observance [7,14,54]. In addition, subjects participating in RCTs are more likely to follow instructions [32,55]. Subjects enrolled in studies tend to pay closer attention to their health. This may minimizing any further advan-

Respiratory Guidelines—Which Real World?

Gary W. K. Wong[1,2], Marc Miravitlles[2,3], Alison Chisholm[2], and Jerry A. Krishnan[2,4]

Ann Am Thorac Soc Vol 11, Supplement 2, pp S85–S91, Feb 2014

RCTs are designed to address the **regulatory** question: "Can this intervention work in an optimized research setting?"

Clinicians, patients, policy makers, insurance companies need answers about the **practical effectiveness** of available management approaches "Which interventions work in which clinical practice setting?"

Moreover, stakeholders also need information on long-term safety, cost and cost-effectiveness.

In the future, healthcare providers will need to be increasingly restrictive about the reimbursement of new expensive drugs, and they will certainly demand solid data with a clear proof of benefit before paying.

S. Burock et al. / European Journal of Cancer 49 (2013) 2777–2783

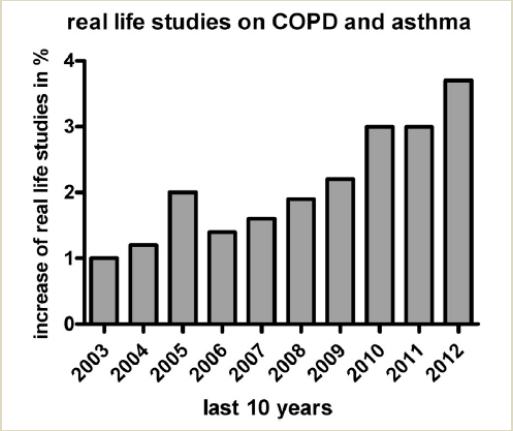
Observational studies have the power and structure to identify areas in which investigation is needed and to test new hypotheses

Table 1 Comorbid and lifestyle factors present in real world patients with asthma who are frequently excluded from classical randomized controlled trial populations

Comorbid disease/lifestyle factor	Prevalence/degree of problem among patients with asthma
Rhinitis and rhinosinusitis	24%–94% (as measured in a range of European and American studies)
	50%–100% (lifetime prevalence)
Anxiety and depression	25%–50% (prevalence in severe and difficult-to-control asthma)
Obesity	Prevalence has increased concurrently with that of asthma over the past decades
GERD	Fivefold higher risk of GERD symptoms in individuals with asthma
	Twofold higher risk of asthma in those with GERD
Smoking	15%–35% (current smokers, wide international variations)
	22%–43% (ex-smokers)
Device misuse	~70%
Real world inhaled corticosteroid adherence	30%–40%

GERD gastroesophageal reflux disease

Curr Allergy Asthma Rep (2011) 11:526–538



Recently the number of real life studies in pharmacological has been rapidly growing in other areas of respiratory medicine, particularly chronic obstructive pulmonary disease (COPD) (Fig. 1).

Pulmonary Pharmacology & Therapeutics 27 (2014) 129–138

A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/ salmeterol in moderate to very severe COPD

Alvar Agustí[1,2], Luis de Teresa[3], Wilfried De Backer[4], Michael T. Zvarich[5], Nicholas Locantore[5], Neil Barnes[6], Jean Bourbeau[7] and Courtney Crim[5]

Eur Respir J 2014; 43: 763–772

adherence

Indeed, mean adherence in both study arms, as assessed by evaluation of inhaler dose counters, was 97.5%, which suggests that the results observed herein reflect those achieved with optimal adherence. Whether such

H-DB 2.2	Percentuale di pazienti in trattamento con statine senza pregresso evento CV o diabete	76,8	77,4	77,6
H-DB 2.3	Percentuale di pazienti senza pregresso evento CV o diabete in trattamento con statine a bassa potenza	41,5	43,7	45,9
H-DB 2.4	Percentuale di pazienti con pregresso evento CV o diabete in trattamento con statine ad alta potenza	62,9	60,9	59,0
H-DB 2.5	Percentuale di pazienti in trattamento con statine aderenti al trattamento	43,5	42,2	40,8
H-DB 2.6	Percentuale di pazienti in trattamento con statine occasionali al trattamento	8,7	9,0	9,4
H-DB 3.1	Percentuale di pazienti in trattamento con farmaci antidiabetici aderenti al trattamento	61,7	61,4	60,1
H-DB 3.2	Percentuale di pazienti in trattamento con DPP-IV inibitori senza i criteri previsti dalle precisazioni sulle limitazioni generali alla rimborsabilità dei DPP-IV inibitori	27,9	35,0	44,4
H-DB 3.3	Percentuale di pazienti con i criteri previsti dalle precisazioni sulle limitazioni generali alla rimborsabilità dei DPP-IV inibitori non in trattamento con DPP-IV inibitori	59,8	67,1	74,4
H-DB 4.1	Percentuale di pazienti con ricovero per BPCO in trattamento con ICS	56,7	56,1	56,2
H-DB 4.2	Percentuale di pazienti con ricovero per BPCO in trattamento con LABA e/o LAMA	54,4	53,4	53,0
H-DB 4.3	Percentuale di pazienti in trattamento con ICS senza esacerbazioni	52,5	52,2	52,2
H-DB 4.4	Percentuale di pazienti in trattamento con farmaci per le sindromi ostruttive delle vie respiratorie aderenti al trattamento	13,9	14,1	13,6
H-DB 4.5	Percentuale di pazienti in trattamento con farmaci per le sindromi ostruttive delle vie respiratorie occasionali al trattamento	61,5	61,4	62,0
H-DB 5.1	Percentuale di pazienti con frattura vertebrale o di femore o in terapia con corticosteroidi in trattamento con farmaci per l'osteoporosi	23,3	25,5	29,3
H-DB 5.2	Percentuale di pazienti in trattamento con farmaci per l'osteoporosi senza pregressa frattura vertebrale o di femore e senza pregressa terapia con corticosteroidi	94,1	95,0	95,0
H-DB 5.3	Percentuale di pazienti in trattamento con farmaci per l'osteoporosi che associano calcio o vitamina D	59,3	53,5	51,1
H-DB 5.4	Percentuale di pazienti in trattamento con farmaci per l'osteoporosi aderenti al trattamento	48,5	48,5	49,5

Data by Italian Drug Agency – AIFA 2014

3. Real life studies

3.1. Real life studies: definition and features

Real life studies have been described in a variety of ways. The European Working Group on Relative Effectiveness has defined real life trials as a way to analyze medical data collected under real life conditions [27]. In essence, they are conducted in everyday settings, and for this reason, they provide insights into the real life effectiveness of a medical condition/intervention.

- no randomization
- confounding factors
- unbalanced groups of pts

Table 2
Types of real life studies.

Type	Characteristics	Application
Databases	• Cross-sectional or longitudinal analysis of previously collected data.	• Retrospective data analysis on various topics.
Population surveys	• Surveys, patient health status and opinion assessment.	• Epidemiological studies.
Patient chart reviews	• In depth evaluation of previously collected data, particularly focusing on diagnosis and treatment.	• Assessment of disease management for planning guidelines.
Registries	• A medical institute record of all patients treated for a specific disease.	• Analysis of a medical centre experience/management/changes in the treatment of a disease.
Observational data	• Prospective or retrospective data collection, usually on population cohorts, over a long follow-up period.	• Examination of medical intervention effectiveness, including safety and tolerability.
Pragmatic trials	• Assesses treatment outcomes in the context of real-life clinical practice.	• Compare interventions under routine clinical circumstances.

The lack of patient selection, one of the most distinctive characteristics of real life studies, makes it impossible to avoid unmeasured confounding factors [11,29], while the absence of blinding and randomization does not always allow factors potentially influencing the outcomes to be properly balanced [14,53,101]. This is particularly

Under real-life conditions, in the absence of randomization, severity of the underlying disease influences treatment decisions [108]. This results in "confounding by indication", meaning that the perception of a different prognosis leads the physician to preferentially prescribe one of the available treatments. As a result, prog-

Original Article | Journal of INTERNAL MEDICINE

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Combination of budesonide/formoterol more effective than fluticasone/salmeterol in preventing exacerbations in chronic obstructive pulmonary disease: the PATHOS study

K. Larsson[1], C. Janson[2], K. Lisspers[3], L. Jørgensen[4], G. Stratelis[4], G. Telg[4], B. Ställberg[3] & G. Johansson[3]

Journal of Internal Medicine, 2013, 273; 584–594

Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting β_2 agonist: observational matched cohort study (PATHOS)

BMJ 2013;346:f3306 doi: 10.1136/bmj.f3306

Table 2 *Yearly occurrence of events among pairwise (1 : 1) propensity score-matched populations of COPD patients treated with budesonide/formoterol versus fluticasone/salmeterol*

Variable	Fluticasone/ salmeterol (n = 2734)	Budesonide/ formoterol (n = 2734)	Treatment contrast[a]	
Events, per patient-year	Mean (95% CI)	Mean (95% CI)	Rate ratio (95% CI)	*P*-value
All exacerbations	1.09 (1.05–1.14)	0.80 (0.77–0.84)	0.74 (0.69–0.79)	<0.0001
COPD hospitalizations	0.21 (0.20–0.23)	0.15 (0.142–0.163)	0.71 (0.65–0.78)	<0.0001
COPD-related hospital stay, days	0.95 (0.88–1.02)	0.63 (0.58–0.67)	0.66 (0.62–0.71)	<0.0001
Emergency visits	0.034 (0.031–0.037)	0.027 (0.025–0.030)	0.79 (0.71–0.89)	0.0003
Oral steroid use	0.85 (0.81–0.90)	0.63 (0.60–0.67)	0.74 (0.68–0.81)	<0.0001
Antibiotic use	0.54 (0.52–0.57)	0.38 (0.37–0.40)	0.70 (0.66–0.75)	<0.0001

- large retrospective studies
- long study period
- depict real-life setting
- Sweden has a reliable/well organized registry system

Table 2| **Pneumonia events by type for pairwise (1:1) propensity score matched populations treated with budesonide/formoterol versus fluticasone/salmeterol for COPD. All P<0.001, Poisson regression**

Measure	Event rate (95% CI) Fluticasone/salmeterol	Budesonide/forme
Diagnosis of pneumonia overall†	11.0 (10.4 to 11.8)	6.4 (6.0 to 6.9
Admission to hospital because of pneumonia†	7.4 (6.9 to 8.0)	4.3 (3.9 to 4.6
Diagnosis of pneumonia in primary care†	4.2 (3.9 to 4.5)	2.7 (2.5 to 2.9
Diagnosis of pneumonia in hospital outpatient care†	1.3 (1.2 to 1.4)	0.7 (0.7 to 0.8
Days in hospital because of pneumonia‡	52.8 (48.9 to 57.0)	29.0 (26.5 to 31

- **in most cases lack of spirometry**
- **no information on severity of COPD**
- **no BMI**
- **no information on adherence to the treatment**
- **no clear whether pneumonias were radiographically confirmed**
- **the study started in 1999 (drugs not available for COPD)**

Rethinking Randomized Clinical Trials for Comparative Effectiveness Research: The Need for Transformational Change

Bryan R. Luce, PhD, MBA; Judith M. Kramer, MD, MS; Steven N. Goodman, MD, MHS, PhD; Jason T. Connor, PhD; Sean Tunis, MD, MSc; Danielle Whicher, MHS; and J. Sanford Schwartz, MD

Ann Intern Med. 2009;151:206-209.

CER

While advances in medical science have led to continued improvements in medical care and health outcomes, evidence of the comparative effectiveness of alternative management options remains inadequate for informed medical care and health policy decision making. The result is frequently suboptimal and inefficient care as well as unsustainable costs. To enhance or at least maintain quality of care as health reform and cost containment occurs, better evidence of comparative clinical and cost-effectiveness is required (1).

- a lot of scientific data
- poor comparative data
- efficacy is not effectiveness

Different inhalers, the same ease of use?
Wrong use, good therapeutic results?

Pragmatic Clinical Trials: RCTs Designed for Decision Makers

A defining objective of CER is to provide information to help patients, consumers, clinicians, and payers make more informed clinical and health policy decisions. However, many RCTs exclude clinically relevant patient subgroups (as defined by age, sex, race, ethnicity, and comorbid conditions), commonly used comparator interventions, important patient outcomes (such as quality of life and longer-term effect), and nonexpert providers (23). These exclusions diminish the relevance of the trial results to some important clinical and policy decisions.







Table 2
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Pragmatic trials	• Assesses treatment outcomes in the context of real-life clinical practice.	• Compare interventions under routine clinical circumstances.

The Salford Lung Study protocol: a pragmatic, randomised phase III real-world effectiveness trial in chronic obstructive pulmonary disease

Nawar Diar Bakerly[1], Ashley Woodcock[2], John P. New[1], J. Martin Gibson[1], Wei Wu[3], David Leather[4] and Jørgen Vestbo[2,5*]

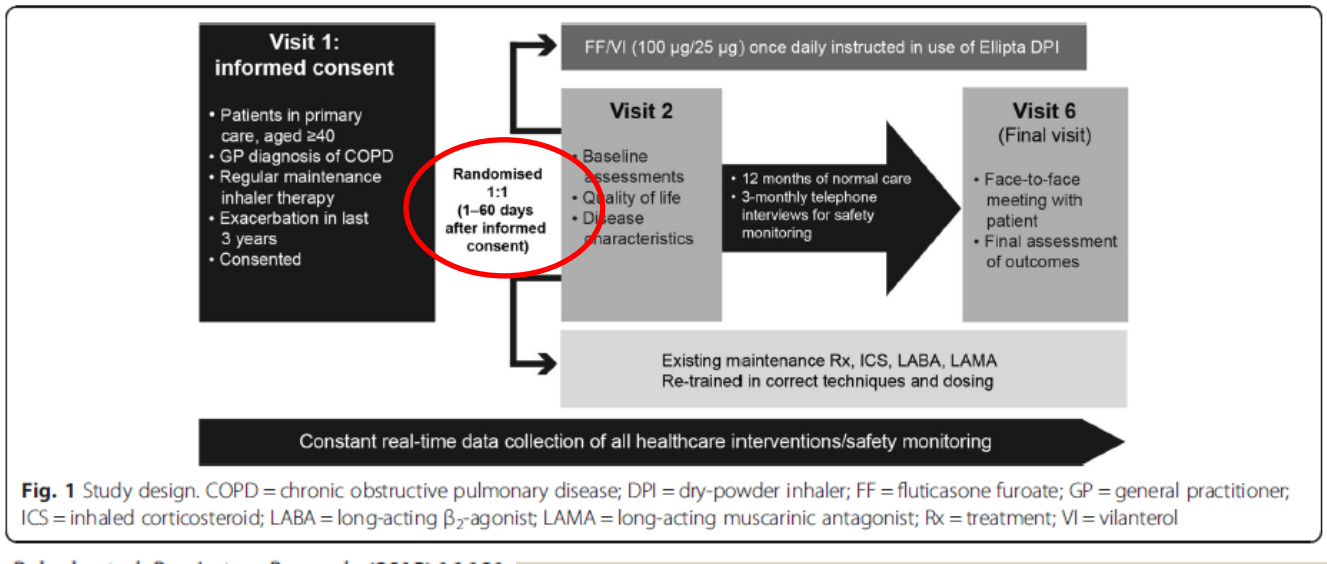

Fig. 1 Study design. COPD = chronic obstructive pulmonary disease; DPI = dry-powder inhaler; FF = fluticasone furoate; GP = general practitioner; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; Rx = treatment; VI = vilanterol

Bakerly *et al. Respiratory Research* (2015) 16:101

Table 1 Study endpoints

Endpoint
Primary endpoint
Mean annual rate of moderate or severe exacerbations
Secondary endpoints
• COPD-related secondary care contacts
• COPD-related primary care contacts
• Time to discontinuation of initial therapy
• Time to addition of a further COPD controller medication
• Time to first moderate/severe exacerbation
• Time to first severe exacerbation (i.e, hospitalisation)
• Adherence to study medication
• Number of salbutamol inhalers collected by the patients from study-enrolled community pharmacies over the 12-month treatment period

Conclusions

- RCTs are the gold standard for providing “efficacy” in selected patients
- Real life data could be of paramount importance, but the lack of randomization makes them useful for hypothesis generation
- Clinicians should know clinical outcomes in a large real life scale
- Payers should pay for practical evidence, not for theory
- Pragmatic studies could represent an interesting tool for practical comparisons with limited bias, also for regulatory purposes