REVIEW
OBSTRUCTIVE LUNG DISEASE

# Observational studies assessing the pharmacological treatment of obstructive lung disease: strengths, challenges and considerations for study design

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ABSTRACT Randomised controlled trials (RCTs) are the gold standard for evaluating treatment efficacy in patients with obstructive lung disease. However, due to strict inclusion criteria and the conditions required for ascertaining statistical significance, the patients included typically represent as little as 5% of the general obstructive lung disease population. Thus, studies in broader patient populations are becoming increasingly important. These can be randomised effectiveness trials or observational studies providing data on real-world treatment effectiveness and safety data that complement efficacy RCTs.

In this review we describe the features associated with the diagnosis of asthma and chronic obstructive pulmonary disease (COPD) in the real-world clinical practice setting. We also discuss how RCTs and observational studies have reported opposing outcomes with several treatments and inhaler devices due to differences in study design and the variations in patients recruited by different study types. Whilst observational studies are not without weaknesses, we outline recently developed tools for defining markers of quality of observational studies. We also examine how observational studies are capable of providing valuable insights into disease mechanisms and management and how they are a vital component of research into obstructive lung disease.

As we move into an era of personalised medicine, recent observational studies, such as the NOVEL observational longiTudinal studY (NOVELTY), have the capacity to provide a greater understanding of the value of a personalised healthcare approach in patients in clinical practice by focussing on standardised outcome measures of patient-reported outcomes, physician assessments, airway physiology, and blood and airway biomarkers across both primary and specialist care.

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**Observational studies can support RCTs in influencing clinical practice in the field of obstructive lung disease** https://bit.ly/36YWu0W

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## Introduction

Intervention trials, such as randomised controlled trials (RCTs), and observational studies, such as registry studies have, until recently, been perceived as being distinct and mutually exclusive approaches to clinical research in respiratory medicine, as well as in other fields of medical research. Classical RCTs aim to establish the safety and efficacy of a treatment in the target patient population [1, 2], whereas classical epidemiology observational studies aim to ascertain how often diseases occur in different groups of people and why [3]. Additionally, epidemiological information is used to prepare and evaluate strategies to prevent illness and as a guide for the management of patients in whom disease has already developed [3]. Real-world observational studies with a prospectively recruited cohort aim to establish the effectiveness and safety of a treatment compared with others in a more general population of patients in a real-world, clinical practice setting, both with and without deliberate manipulation or intervention [1]. Furthermore, real-world studies enable exploratory research in broad patient populations that can be used to generate hypotheses, improve understanding of various aspects of disease and treatments, provide novel perspectives and challenge existing paradigms [1, 4].

The aim of this review is to evaluate the strengths and limitations of existing observational studies in assessing the effectiveness of pharmacological treatment in asthma and/or chronic obstructive pulmonary disease (COPD), in order to highlight key considerations for ongoing and future observational studies in obstructive lung disease.

### *Comparing RCTs with observational real-world studies*

Observational studies and classical efficacy RCTs ask distinct research questions and thus employ different study methodologies and patient populations to answer them. Classical efficacy RCTs aim to compare the efficacy and safety of treatments within a patient population selected using strict inclusion criteria (*e.g.* exclusion of active smokers), with high disease severity (in terms of lung function impairment), good treatment adherence and good inhaler technique, thereby tightly controlling confounding factors. Although this level of internal validity and control makes it easier to identify the absolute benefit or lack of benefit of a treatment, it comes at the cost of external validity [5]; thus, results from efficacy RCTs may not be broadly generalisable to the wider population of patients with obstructive lung disease. Indeed, while RCTs remain the gold standard for evaluating treatments [2], the patients they include can represent as few as 5% of the general asthma/COPD population [6, 7].

In contrast, pragmatic RCTs aim to assess the differential benefit of a treatment in a broader patient population (*e.g.* patients with less severe lung function impairment and more comorbidities) in a normal ecology of care and with less intensive medical supervision compared with efficacy RCTs [8]. However, pragmatic RCTs still involve a higher organisation of clinical practice than that expected in a real-world setting.

With less intervention and organisation than efficacy RCTs or pragmatic RCTs, pure observational studies offer a more practical and cost-effective means to investigate the long-term outcome of a treatment in a broader patient population than that included in an RCT [5, 8].

As real-world studies differ substantially from efficacy RCTs in their objectives and approach, their study design often requires different considerations and many more patients are eligible for both pragmatic RCTs and observational studies compared with efficacy RCTs [1]. Such studies are seen as increasingly important for understanding treatment effectiveness in a broader patient population [8–11], thereby potentially informing future treatment management strategies.

Real-world studies can take many forms, including the following.

Classical epidemiological studies, *e.g.* trajectories of lung function in COPD [12], assessing the association between sleep-disordered breathing and asthma [13] management, morbidity and mortality of COPD in Sweden [14] and identifying COPD subtypes and corresponding biomarkers [15].

Retrospective studies using existing, routinely collected health data, such as electronic medical records or insurance claims, *e.g.* a study on predicting asthma attacks using real-world primary care data in the UK [16].

Post-marketing surveillance/phase IV studies monitor the real-world response to newly approved treatments, including real-world safety and mortality. These studies have helped identify and understand events such as the increased mortality rates observed amongst patients with asthma who received salbutamol (in Australia) and fenoterol (in New Zealand) during the 1980s [17–19].

Comparative effectiveness or safety studies assess the differential benefit of a treatment in broad patient categories to inform a clinical or policy decision by providing evidence for adoption of the intervention

into a real-world setting [20, 21]; *e.g.* The Salford Lung Study (a pragmatic RCT) [9, 10, 22], the Novel START study [23] and the Lung Health Study [24].

In practical terms, real-world studies complement results from RCTs by providing a higher external validity once the efficacy and safety of a treatment has been confirmed under the strictly controlled conditions of an RCT [5, 8]. Tools, such the PRECIS-2, are available to describe the representativeness of a clinical trial compared with a real-world setting and are a valuable resource [25]. In addition, observational studies can be used to investigate aspects that RCTs cannot, such as prevalence and incidence of disease, aetiology, defining prognoses, disease impact, and burden and cost-effectiveness of treatment. Table 1 shows select examples of findings from real-world asthma and COPD data highlighting the different research questions that can be asked from pure observational studies and pragmatic trials covering treatment choice, the use of inhalers, biomarkers and clinical disease history.

### *Principal causes and factors associated with forced expiratory volume in 1 s decline, COPD and asthma, as established from observational studies*

The principal causes and factors associated with forced expiratory volume in 1 s ($FEV_1$) decline, COPD and asthma, as established from previous observational studies, are listed in table 2. Carefully conducted longitudinal studies have been instrumental in establishing causal relationships in obstructive lung disease, with case–control and cohort studies in the 1950s and 1960s firmly establishing cigarette smoking as the single greatest risk factor for lung cancer [48–50]. More recently, ECLIPSE (Evaluation of COPD longitudinally to identify predictive surrogate endpoints), a longitudinal study, was devised with the aim of describing the subtypes of COPD, defining predictive or surrogate markers of disease progression and, potentially, novel targets for therapeutic intervention [15].

Despite having plateaued and even fallen in some regions, globally the prevalence of asthma has been increasing rapidly for several decades [51]. There is a strong genetic component in asthma, demonstrated by concordance of approximately 50% in monozygotic twins with asthma [52]; however, the speed of the increase in prevalence is thought to be too high to be accounted for by a genetic change alone and is therefore more likely to be related to environmental changes [53].

## Comparing guidelines, RCTs and observational study outcomes in obstructive lung disease

### *Treatment options*

Results from RCTs have indicated a benefit of adding low-dose oral theophylline to inhaled corticosteroid (ICS) therapy for COPD [94, 95]; however, UK National Institute for Health and Care Excellence (NICE) guidelines for COPD do not recommend theophylline as the first-choice of treatment [96], and the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) report states that there is only limited and contradictory evidence for the use of low-dose theophylline [97]. In addition, results from the TWICS (theophylline with inhaled corticosteroids) pragmatic trial found no benefit of theophylline added to ICS over placebo in a real-world setting [46]. Similarly, a systematic review of RCTs for asthma demonstrated the superiority of ICS over leukotriene receptor antagonists (LTRA) for the management of asthma [98]; however, the ELEVATE (A pragmatic randomised single-blind controlled trial and economic evaluation of the use of leukotriene receptor antagonists in primary care at steps 2 and 3 of the national asthma guidelines) pragmatic study found no difference in effectiveness between ICS and LTRA [45]. These seemingly conflicting findings may be due, in part, to the different patient populations included and the lower adherence rate with ICS *versus* LTRA [45, 99].

In terms of treatment reduction, the Global Initiative for Asthma (GINA) recommends stepping down ICS/long-acting $\beta_2$-agonist (LABA) dose once asthma control has been achieved for $\geqslant$3 months [100]. However, the FFLUX (A randomised pragmatic trial of changing to and stepping down fluticasone/formoterol in asthma) pragmatic trial that investigated the stepping-down of treatment in patients who were stable following 12 weeks of treatment, found that patients with a history of one or two exacerbations within 12 months prior to starting treatment were at increased risk of re-exacerbation [44]. This highlights the need for research beyond the outcomes of efficacy RCTs to be considered when guidelines are developed and in this specific case, the need for asthma exacerbation history to be considered in guiding clinicians in stepping-down of treatment.

Until relatively recently, the recommended treatment for asthma has been ICS maintenance treatment with as-needed short-acting $\beta_2$-agonists (SABAs) [101]. However, real-world data have found that patients typically underuse ICS and overuse SABA [102]. This has led to the observation that overuse of SABA is associated with an increase in all-cause mortality risk in patients with asthma [103]; the subsequent revision of the guidelines to recommend combined ICS/SABA as needed demonstrates how the outcomes of observational studies are influencing global guidelines [100].

TABLE 1 Examples of findings from real-world asthma and COPD data highlighting the different research questions that can be asked from pure observational studies and pragmatic trials

| Authors and study name | Question and/or comparators | Patient population | Ecology of care | Findings |
|---|---|---|---|---|
| **Pure observational studies** | | | | |
| **Treatment choice** | | | | |
| Buhl *et al.* [26] DACCORD study | **Question:** What is the comparative effectiveness of dual bronchodilation *versus* triple therapy in COPD? **Comparator:** Dual *versus* triple bronchodilation therapy | • ⩾40 years initiating or switching maintenance therapy.<br>• Diagnosed with COPD confirmed by spirometry.<br>• Patients who had participated in asthma disease management programme were excluded. | • Prospective observational study.<br>• No intervention beyond data-taking and standard care. | • More patients on triple therapy experienced exacerbation and had significantly less clinical improvement.<br>• Exacerbation rate was highest in patient who was already on triple therapy. |
| Kardos *et al.* [27] DINO and DACOTA studies | **Question:** What is the real-world effectiveness of roflumilast add-on treatment in reducing clinical symptom score in patients with severe to very severe COPD? **Comparator:** 6 months after initiation *versus* time of initiation. | • Patients with severe to very severe COPD.<br>• Patients eligible for roflumilast treatment as indicated on drug label.<br>• No previous roflumilast treatment. | • Prospective, observational study<br>• No intervention beyond consent-taking and measurement. | • Roflumilast add-on treatment associated with significant reduction in symptom score 6 months after initiation. |
| **Mixed inhaler devices** | | | | |
| Rhee *et al.* [28] HIRA study | **Question:** Does changing inhaler device from DPI to pMDI for FDC ICS/LABA delivery impact real-world asthma outcome? **Comparator:** Changing to pMDI *versus* remaining on DPI. | • 12–80 years.<br>• ⩾2 prescriptions of FDC ICS/LABA DPI and no pMDI prescription at baseline.<br>• Change to same ICS dose as baseline dosage.<br>• Have not received multiple different FDC ICS/LABA or separate ICS and LABA at index date. | • Historical cohort study.<br>• No intervention. | • Changing to pMDI led to non-inferior asthma exacerbation rate *versus* remaining on DPI. |
| Bosnic-Anticevich *et al.* [29] | **Question:** Does prescribing multiple inhaler devices requiring different inhalation techniques result in worse clinical outcomes in COPD patients? | • ⩾40 years from primary care record.<br>• Coded diagnosis for COPD. | • Historical cohort study.<br>• No intervention. | • Patients prescribed with mixed inhaler devices (DPI and pMDI) for reliever and controller therapy had higher COPD exacerbation rate *versus* patients with similar inhaler devices. |
| Price *et al.* [30] | **Question:** What is the comparative effectiveness of initiating with the same BAI device for asthma controller and reliever therapy *versus* mixed BAI and pMDI for primary care patients? | • 4–80 years from primary care record.<br>• Had coded diagnosis for asthma, ⩾2 prescriptions for asthma in the past year (baseline), or ⩾2 prescriptions for asthma, including one ICS, at one year after initiation (index date).<br>• Excluded patients >60 years who smoked, patients with other chronic respiratory diseases, patients who received asthma controller therapy at baseline or LABA at index date. | • Historical cohort study.<br>• No intervention. | • Patients prescribed the same device for reliever and controller therapy had significantly better asthma control and lower risk of severe exacerbations. |

Continued

TABLE 1 Continued

| Authors and study name | Question and/or comparators | Patient population | Ecology of care | Findings |
|---|---|---|---|---|
| **Pure observational studies** | | | | |
| **Inhaler device type** | | | | |
| PRICE *et al.* [31] | **Question:** What is the comparative effectiveness of pMDI *versus* DPI for delivery of FP/SAL FDC ICS/LABA in routine primary care population? **Comparator:** FP/SAL pMDI *versus* FP/SAL DPI. | • 4–80 years from primary care record.<br>• Coded diagnosis of asthma or ⩾2 prescriptions for asthma medication (⩾1 ICS) at 1-year baseline.<br>• ⩾1 prescriptions for asthma at baseline.<br>• Excluded patients with a diagnosis code for other respiratory diseases. | • Historical cohort study.<br>• No intervention. | • Patients prescribed pMDI for FP/SAL had significantly higher odds of achieving asthma control and treatment success *versus* DPI. |
| JONES *et al.* [32] | **Question:** What is the comparative effectiveness among patients with COPD initiating FP/SAL *via* pMDI *versus* DPI in a real-world setting? **Comparator:** FP/SAL pMDI *versus* FP/SAL DPI. | • ⩾35 years from primary care record.<br>• Coded diagnosis for COPD, $FEV_1/FVC$ <0.7, and ⩾2 prescriptions of FP/SAL.<br>• Excluded patients with chronic respiratory disorder aside from COPD, asthma or bronchiectasis.<br>• Excluded patients receiving maintenance OCS or ICS at baseline. | • Historical cohort study.<br>• No intervention. | • Patients prescribed 500 µg/day FP/SAL delivered *via* pMDI had significantly fewer moderate to severe exacerbations *versus* DPI.<br>• No difference observed in patients prescribed 1000 µg/day FP/SAL. |
| **Inhaler technique** | | | | |
| SULAIMAN *et al.* [33] | **Question:** What is the prevalence of inhaler usage errors, in terms of technique and timing of usage, over time in patients with asthma or COPD? | • Patients with asthma or COPD prescribed twice-daily preventer inhaler.<br>• Recruited from random general practices and community pharmacies across Ireland. | • Prospective observational study.<br>• Patients were aware that they were given an inhaler that incorporated an audio recording device. | • Based on the audio recording of inhaler usage, only a minority of patients had good inhaler technique and used their inhalers at the correct dosing intervals through the entire follow-up. |
| OCAKLI *et al.* [34] | **Question:** Do inhaler technique errors occur differently between asthma and COPD patients, and what factors are associated with poor inhaler technique? | • >18 years with asthma and COPD, using inhalers for ⩾1 month.<br>• Recruited from tertiary pulmonology clinic. | • Cross-sectional observational survey study.<br>• Patient interaction limited to survey-taking and inhaler technique demonstration. | • Several device-specific errors were more common in patients with asthma than COPD.<br>• Errors were associated with female gender, shorter duration of disease and shorter duration of inhaler use. |
| MELANI *et al.* [35] GENEBI project | **Question:** What is the prevalence of, and factors associated with, inhaler technique errors in outpatients referred to chest clinics, and what is the association between inhalation technique and clinical outcomes? | • >14 years old regularly using inhaler.<br>• Recruited from chest clinics throughout Italy. | • Cross-sectional survey study.<br>• Patient interaction limited to survey-taking and inhaler technique demonstration. | • Inhaler technique errors were common in all studied device types.<br>• Inhalation technique errors were associated with higher healthcare utilisation and poorer clinical control in patients with both asthma and COPD. |

Continued

TABLE 1 Continued

| Authors and study name | Question and/or comparators | Patient population | Ecology of care | Findings |
|---|---|---|---|---|
| **Pure observational studies** | | | | |
| PRICE *et al.* [36] CRITIKAL study | **Question:** What is the association between specific inhaler errors and asthma outcomes? | • >16 years old with asthma.<br>• Receiving FDC ICS/LABA *via* DPI or pMDI.<br>• Excluded patients with other respiratory diseases.<br>• Excluded patients who had received OCS or antibiotics in the past 2 weeks, or long-term systemic treatment for asthma. | • Cross-sectional survey study.<br>• Patients undergoing asthma review including questionnaire and inhaler technique assessment in primary care clinics. | • Inhaler technique errors were common, regardless of device type.<br>• Several errors were critical errors associated with poorer asthma control. |
| **Biomarkers** | | | | |
| ZEIGER *et al.* [37] PREDUNA study | **Question:** Is higher blood eosinophil count a risk factor for future exacerbations in patients with persistent asthma? | • 18–64 years.<br>• Patients with ⩾2 years of persistent asthma.<br>• Excluded patients with COPD and other selected chronic diseases. | • Historical cohort study.<br>• No intervention. | • Higher blood eosinophil count was a risk factor for higher risk and increased rate of future asthma exacerbations and increased SABA use. |
| ZEIGER *et al.* [38] | **Question:** Does adding $F_{eNO}$ assessment to standard asthma management in specialist care improve asthma control in patients with severe uncontrolled asthma? | • ⩾12 years.<br>• Diagnosis code for asthma and dispensed maintenance therapy.<br>• No other chronic respiratory disease in the past 3 years.<br>• No visit to the clinic of the other intervention arm during follow-up. | • Prospective, observational study.<br>• Patients were managed under standard care, with the addition of $F_{eNO}$ measurement for patients in the $F_{eNO}$-assisted care arm. | • Patients from $F_{eNO}$-assisted centres had similar risk of developing asthma exacerbation or using ⩾7 SABA canisters during follow-up *versus* patients receiving standard care only.<br>• Asthma exacerbation rate was lower in patients with aeroallergen sensitisation in the $F_{eNO}$-assisted care group *versus* other groups. |
| KERKHOF *et al.* [39] | **Question:** Is there an association between blood eosinophil count during a stable COPD period and future exacerbation rate in a broad COPD population? | • ⩾40 years from primary care record.<br>• Coded diagnosis for COPD,<br>• $FEV_1$/FVC <0.7 within the past 5 years.<br>• History of smoking and no other chronic respiratory disease. | • Historical cohort study.<br>• No intervention. | • Elevated blood eosinophil count was associated with higher exacerbation rate.<br>• Association was limited to ex-smokers. |
| PRICE *et al.* [40] | **Question:** What is the association between blood eosinophil count and prospective asthma outcomes in the general asthma population? | • 12–80 years from primary care record.<br>• Coded diagnosis of asthma.<br>• Excluded patients with other chronic respiratory disease or lacking information on smoking status. | • Historical cohort study.<br>• No intervention. | • Patients with high blood eosinophil count had significantly more severe asthma exacerbations and significantly lower odds of achieving asthma control. |
| **Clinical history of disease** | | | | |
| JONES *et al.* [41] | **Question:** What are the patterns of healthcare utilisation and comorbidities in the years leading to diagnosis of COPD which represent missed opportunities to diagnose COPD? | • ⩾40 years from primary care record.<br>• Recorded diagnosis of COPD and ⩾2 prescriptions for COPD-related drugs following diagnosis. | • Historical cohort study.<br>• No intervention. | • Mean primary and secondary care lower respiratory consultation increased during the 20 years prior to COPD diagnosis, especially in the 5 years prior to diagnosis. |

Continued

TABLE 1 Continued

| Authors and study name | Question and/or comparators | Patient population | Ecology of care | Findings |
|---|---|---|---|---|
| **Pure observational studies** | | | | |
| Veenendaal *et al.* [42] | **Question:** What is the prevalence of age- and sex-specific chronic comorbidities in a real-world population of general practice patients with asthma? | • ⩾16 years.<br>• Diagnosis of active asthma. | • Historical cohort study.<br>• No intervention. | • Majority patients had ⩾1 comorbidity.<br>• Cardiovascular comorbidities were the most prevalent followed by endocrinal and digestive.<br>• Female patients had, in general, more comorbidities.<br>• Some comorbidities were more commonly found in either sex- or age-specific groups. |
| Wang *et al.* [43] ISAR study | **Question:** What are the demographic and clinical characteristics of an international (USA, Europe and Asia/Pacific) population of patients with severe asthma? | • ⩾18 years.<br>• Receiving GINA Step 5 treatment or uncontrolled whilst receiving GINA Step 4 treatment | • Retrospective and prospective study.<br>• No intervention. | • There was substantial heterogeneity in the clinical characteristics of patients with severe asthma between countries.<br>• More work is required to definitively explain many of these differences. |
| **Pragmatic trials** | | | | |
| **Treatment choice** | | | | |
| Usmani *et al.* [44] FFLUX trial | **Question:** What is the impact of stepping-down FP/FOR FDC ICS/LABA dosage on asthma control in a real-world setting? **Comparator:** Maintaining FP/FOR (1000/40 µg) *versus* stepping down to 500/20 µg. | • 18–75 years.<br>• Diagnosis of asthma.<br>• Must have demonstrated sufficient inhaler technique.<br>• Recruited from multiple primary care centres across England.<br>• Excluded patients with other chronic respiratory diseases, those who had severe asthma or uncontrolled asthma prior to recruitment. | • Open-label trial.<br>• Patients receive a change of inhaler followed by dose step-down.<br>• Patients may have received inhaler technique training.<br>• Adherence was calculated based on dose counter values. | • Stepping down FP/FOR dosage did not significantly compromise asthma control after 12 weeks.<br>• Patients with a history of asthma exacerbation were at greater risk of further exacerbations after stepping down treatment. |
| Price *et al.* [45] ELEVATE trial | **Question:** What is the effectiveness of LTRA *versus* ICS as initial asthma controller therapy in a real-world setting? **Comparator:** LTRA *versus* ICS.<br><br>**Question:** What is the effectiveness of LTRA *versus* LABA as add-on therapy in patients with uncontrolled asthma despite ICS in a real-world setting? **Comparator:** LTRA *versus* LABA. | • 12–80 years.<br>• Physician diagnosis of asthma.<br>• Pre-bronchodilation PEF % predicted >50%.<br>• Questionnaire assessed impairment in asthma-related quality of life or asthma control. | • Patients provided with individualised asthma action plan.<br>• Patients taking disallowed drug remained in the study.<br>• Separate intention-to-treat and per protocol analyses. | • LTRA was equivalent to ICS as the initial controller therapy in terms of quality of life.<br>• Patients who initiated with LTRA had numerically, but not significantly, higher adherence rate.<br>• LTRA was equivalent to LABA as the add-on therapy in terms of quality of life.<br>• Patients initiated with LTRA had a significantly higher adherence rate to treatment. |

Continued

TABLE 1 Continued

| Authors and study name | Question and/or comparators | Patient population | Ecology of care | Findings |
|---|---|---|---|---|
| **Pragmatic trials** | | | | |
| DEVEREUX *et al.* [46] TWICS trial | **Question:** Does adding low-dose theophylline to ICS treatment reduce the risk of exacerbations in a broad population of patients with a demonstrated history of COPD? **Comparator:** Low-dose theophylline *versus* placebo. | • ⩾40 years.<br>• Coded diagnosis of COPD, $FEV_1$/FVC <0.7.<br>• Smoking history of >10 pack-years.<br>• Currently using ICS.<br>• ⩾2 exacerbations in the previous year.<br>• Excluded patients with other chronic respiratory diseases, ischaemic heart disease or under drugs which may influence plasma theophylline level. | • Double-blinded placebo-controlled trial.<br>• No other change in patient care other than receiving theophylline/ placebo. | • Addition of low-dose oral theophylline to ICS treatment did not significantly reduce COPD exacerbations *versus* placebo. |
| VESTBO *et al.* [10] Salford Lung Study | **Question:** What is the effectiveness of initiating open-label, once-daily FF/VI in DPI over existing therapy in real-world population of patients with COPD treated with standard care in a general practice setting? **Comparator:** FF/VI DPI *versus* standard care. | • ⩾40 years.<br>• Documented diagnosis of COPD.<br>• ⩾1 COPD exacerbation in the last 3 years.<br>• Receiving regular maintenance inhaled therapy.<br>• No restriction on smoking status or lung function.<br>• No exacerbations during the past 2 weeks.<br>• No long-term OCS use. | • Open-label trial.<br>• Primary care setting.<br>• Patients allowed to continue previous LAMA treatment.<br>• Patients trained for correct inhaler usage and technique.<br>• Patients in standard care not permitted to switch to FF/VI.<br>• Trial staff and doctors received training on trial procedures.<br>• Patients managed under standard care. | • Patients initiated on FF/ VI had a significantly lower rate of moderate to severe COPD exacerbations *versus* standard care.<br>• There was no difference in the rate of serious adverse events. |
| WOODCOCK *et al.* [9] Salford Lung Study | **Question:** What is the effectiveness of initiating open-label, once-daily FF/VI in DPI *versus* existing asthma maintenance therapy using pragmatic RCT design? **Comparator:** FF/VI DPI *versus* standard care. | • ⩾18 years.<br>• Diagnosed with asthma in primary care.<br>• Receiving regular maintenance inhaler therapy.<br>• No history of COPD.<br>• No restriction on smoking status or lung function. | • Open-label trial.<br>• Primary care setting.<br>• Patients trained for correct inhaler technique.<br>• Patients managed under standard care.<br>• Patients allowed to modify treatment, aside from initiating FF/VI within the standard care group.<br>• Trial staff and doctors received training on trial procedures. | • Patients initiated on FF/ VI were significantly more likely to achieve asthma control compared with usual care.<br>• There was no difference in the rate of serious adverse events. |
| **Biomarkers** | | | | |
| PRICE *et al.* [47] NSRS study | **Question:** What is the value of $F_{eNO}$ in predicting response to extrafine ICS in patients with non-specific respiratory symptoms? | • 18–80 years.<br>• Patients had non-specific persistent respiratory symptoms.<br>• Never diagnosed or received treatment for asthma or other chronic respiratory diseases.<br>• <20% bronchodilator reversibility. | • Double-blind, placebo-controlled trial.<br>• Patients managed under routine care similar to patients with suspected asthma.<br>• Analysed per protocol. | • There was a significant interaction between $F_{eNO}$ level and change in asthma control measure following treatment with extrafine ICS, suggesting $F_{eNO}$ as a valuable marker to predict ICS response in patients with non-specific respiratory symptoms. |

BAI: breath-actuated inhaler; COPD: chronic obstructive pulmonary disease; DPI: dry powder inhaler; FDC: fixed-dose combination; $F_{eNO}$: fractional exhaled nitric oxide; $FEV_1$: forced expiratory volume in 1 s; FF/VI: fluticasone furoate/vilanterol; FOR: formoterol; FP: fluticasone propionate; FVC: forced vital capacity; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; LABA: long-acting $\beta_2$-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene-receptor antagonist; OCS: oral corticosteroid; pMDI: pressurised metred-dose inhaler; PEF: peak expiratory flow; RCT: randomised controlled trial; SABA: short-acting $\beta_2$-agonist; SAL: salmeterol.

TABLE 2 The principal causes and factors associated with $FEV_1$ decline, COPD and asthma, as established from observational studies

| Cause | Effect on $FEV_1$ decline and/or COPD |
|---|---|
| 1. Smoking | • The only environmental risk factor whose contribution to COPD is entirely undisputed [48–50]; up to half of all smokers eventually develop fixed airflow limitation [54].<br>• Smoking during pregnancy increases risk of low birth weight and decreased lung function at birth, leading to lower maximum $FEV_1$ and increased risk of impaired pulmonary function and developing COPD in later life [55–58].<br>• Adolescents who smoke show reduced development of lung function [59]. |
| 2. Occupational exposure to dust and gases | • Leads to accelerated decline in $FEV_1$ and increased incidence of COPD [60–62].<br>• Dose–effect relationship between the number of agents to which subjects were exposed and decline in $FEV_1$ [63]. |
| 3. Burning of solid fuels/biomass | • Linked to an increased risk of developing respiratory symptoms and airflow limitation [64, 65]; rate of $FEV_1$ decline slower and more homogeneous *versus* smokers [66]. |
| 4. Socioeconomic status and poverty | • Strong risk factor for obstructive lung disease [67–69].<br>• Specific link not known, but likely to include multiple aspects throughout life, including environment, diet, housing conditions and other lifestyle and occupational factors [70]. |
| 5. Chronic bronchitis | • Strong association between chronic bronchitis/chronic mucus hypersecretion and $FEV_1$ decline, COPD-related morbidity and both overall and COPD-related mortality [71–73].<br>• Most important in patients <50 years of age [74]. |
| 6. Airway hyper-responsiveness | • Known independent risk factor for COPD [75, 76].<br>• Occurrence during young adult life associated with an increased risk of COPD 20 years later [75]. |
| 7. Asthma | • Uncontrolled asthma leads to airway remodelling and fixed airflow obstruction that may lead to an incorrect diagnosis of COPD [77] . |
| **Cause** | **Effect on asthma** |
| 1. Exposure to microorganisms | • Viral infection is one of the most common causes of asthma exacerbations [53].<br>• Exposure in early life is associated with an increased risk of developing persistent asthma in later life [53]; however, reduced exposure during childhood may be contributing to the global increase in allergy and asthma [52]. |
| 2. Allergen exposure | • Childhood asthma is typically attributed to an allergic sensitisation [52, 53].<br>• The risk of allergic sensitisation may differ between allergens and may be related to the dose and duration of exposure [52, 53, 78]. |
| 3. Smoking (active and passive) | • Passive smoking, both pre- and post-natal, is associated with an increased risk of asthma in children [79].<br>• Passive smoking is also associated with a higher prevalence of asthma and bronchial responsiveness in adults [80].<br>• An association between active smoking and onset of asthma may be stronger in younger than older adults [81]. |
| 4. Air pollution | • Exposure to traffic-related air pollution during early childhood is associated with a higher risk of developing asthma in later life [53].<br>• An association between outdoor nitrogen levels and the onset of asthma has been observed in adults [82]. |
| 5. Indoor environment | • Dampness in residential buildings has been associated with the onset of asthma in both children [83] and adults [84]; this problem may well extend to the workplace [84]. |
| 6. Occupation | • Occupational exposure is estimated to account for approximately 15% of new asthma diagnoses in adults [85].<br>• Cleaners, welders and farm workers in particular are at increased risk [86–88]. |
| 7. Diet | • Low intake of vitamin C and fruit has been associated with a higher risk of asthma [89].<br>• A lower prevalence of wheeze and risk of asthma has been observed in children receiving a Mediterranean diet and fish in early childhood [89]. |
| 8. Obesity | • Obesity is a risk factor for developing asthma in both children and adults [90, 91].<br>• The mechanism is not completely understood, but obesity-induced systemic inflammation [90, 92] and decreased physical activity may both play a role [93]. |

COPD: chronic obstructive pulmonary disease; $FEV_1$: forced expiratory volume in 1 s.

Real-world data may also provide complementary evidence to support findings from RCTs. The Salford Lung Study pragmatic trial successfully demonstrated the real-world effectiveness of fluticasone furoate/vilanterol treatment for maintenance therapy of COPD [10] and asthma [9], adding to the findings from previous RCTs.

Some studies have also suggested limited value or even harm of certain therapies in COPD. An observational nested case–control study of patients with COPD being treated with LABA and ICS from

registry data over 4.5 years found that the addition of the long-acting muscarinic antagonist (LAMA) tiotropium was associated with an increased cardiovascular risk in patients with COPD [104]. However, none of the recent fixed triple combination registration trials have seen this effect and in the three-year ASCENT (Evaluate the effect of aclidinium bromide on long-term cardiovascular safety and exacerbations in moderate to very severe COPD patients) RCT of patients with COPD and high cardiovascular risk, there was no increase in the risk of cardiovascular events for patients receiving the LAMA aclidinium compared with placebo [105].

### *Inhaler device, technique and adherence*

RCTs typically ensure that patients demonstrate correct inhaler technique and adhere to their treatment; thus, results from RCTs reflect the efficacy of inhalers under a near-perfect technique and adherence rate [106, 107]. However, inhalation errors in a real-world setting have been shown to increase the risk of poor treatment outcomes, such as hospitalisation, medication use and symptom control [35, 36, 107]. In addition, mixing inhaler devices may lead to worse COPD outcomes than when single devices or devices requiring the same inhalation technique are used [29, 30]. Thus, results from real-world studies emphasise the importance of ensuring proper inhaler technique to maximise treatment success in both asthma and COPD. Other examples of findings from real-world evidence in asthma/COPD can be found in table 1.

With regard to specific inhaler types, according to the recommendations of the British Thoracic Society Scottish Intercollegiate Guidelines Network [108] and results from interventional RCTs, dry powder inhalers (DPI) are as effective as pressurised metered-dose inhalers (pMDI) for the delivery of ICS treatment [109, 110]. This is supported by a recent study utilising the Korean Health Insurance Claims database, which found a comparable clinical and cost efficiency between patients with asthma who switched from a DPI to a pMDI *versus* patients who remained on a DPI [28]. However, other results have been more conflicting [35, 36, 106, 107, 111] and real-world studies from the UK have suggested that pMDIs are superior to DPIs in both asthma [31] and COPD [32], illustrating that the outcomes of observational studies can still be conflicting and the importance of understanding the different methodologies and analyses used.

### *Weaknesses of observational studies*

It is important to note that despite the many advantages of observational studies, as with all study designs, the methodologies employed are subject to specific biases, including selection bias (systematic differences between baseline characteristics of the groups that are compared) and detection bias (systematic differences between groups in how outcomes are determined) [112]. Studies utilising electronic health records are further susceptible to a degree of inaccuracy and incompleteness; such records are typically collected for routine medical purposes and can lack the quality, detail and accuracy typically required for research purposes [113].

In enrolling a broad patient population, the analysis of data generated from observational studies is complicated by confounding factors such as confounding by indication; *i.e.* most patients receiving medication in an observational study have been formerly diagnosed by a doctor whereas those without the medication have not, despite otherwise appearing almost identical [114]. Another factor which must be considered is the avoidance of immortal time balance, which can be the consequence of incorrect handling of the period between study entry and treatment initiation in time-to-event analyses [115]. For time-dependent confounders, such as body mass index, which is a risk factor for asthma that may lead to reduced physical activity and is also affected by prior levels of physical activity, the parametric g-formula can be used in place of conventional regression approaches [116, 117].

Biases in observational studies can be significantly reduced by using a prospective study design and a predefined statistical analysis plan [5, 118]. In addition, tools such as the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) [119] and Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies [120] may also be beneficial in minimising bias. However, while statistical adjustment and matching can be used to minimise confounding effects [5, 118], factors which are not accounted for, and thus not recorded within the study, are likely to remain. It should be noted that RCTs are often also affected by bias, such as selection and information bias, although this is not always recognised.

### *Markers of quality for observational studies*

Despite their shortcomings, clinical guidelines still place a greater emphasis on results from classical RCTs than from observational studies [8]. Indeed, traditional tools for rating quality of studies such as the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) also downgrade observational study designs [8].

To achieve greater integration of real-world evidence into the development programmes of new drugs, it is vital that observational studies are subjected to standards that are as equally rigorous as those devised for classical RCTs [8]. There is, therefore, a need to standardise the quality of real-world evidence. Recently, a joint task force between the Respiratory Effectiveness Group and the European Academy of Allergy and Clinical Immunology (EAACI) developed a standardised tool for quality appraisal of comparative effectiveness studies, the REal Life EVidence AssessmeNt Tool (RELEVANT; www.regresearchnetwork.org/relevant-tool-2) [121]. The tool incorporates 21 quality checklist items, of which 11 primary items determine a study's suitability for guideline development and 10 secondary items are for general appraisal of the study. Quality appraisal using the RELEVANT tool on selected examples of comparative effectiveness studies are presented in table 3; similar tools are already available for evaluating observational studies [122, 123].

### *Why we need both RCTs and observational studies*

Comparing RCT and observational study data by adjusting and aligning patient data has further highlighted the importance of using both study types to assess the effect of a treatment. A number of studies on the use of statins in patients with COPD have indicated that statins may provide additional benefits in terms of improving lung function and reducing risk of exacerbation, hospitalisation and death [124–126], potentially through reduction of inflammation [127]. Of particular interest, the STATCOPE (Simvastatin for the prevention of exacerbations in moderate-to-severe COPD) RCT found that statins had no impact on exacerbation risk, lung function, or on general or disease-specific quality of life in patients with COPD [128]. In contrast, an observational study by Ingebrigtsen *et al.* [129] found that statins did reduce exacerbation risk. However, when these same observational data were adjusted to align the patients with those from the STATCOPE RCT, statins were found to provide no additional benefit in patients with COPD. Due to the inherent differences in the patient populations of RCTs and observational studies, as previously described, this finding clearly demonstrates why both RCTs and observational studies are needed to form a complete picture of treatment effect.

## Future prospects in real-world evidence in asthma/COPD

Several complex observational studies in asthma/COPD have contributed to a greater understanding of the heterogeneity of the asthma/COPD population in a real-world setting, including COPDGene [130], ECLIPSE [15], SPIROMICS (Subpopulations and intermediary outcomes in COPD study; U-BIOPRED: Unbiased biomarkers in prediction of respiratory disease outcomes) [131] and U-BIOPRED [132]. These studies have led to an increasing recognition of the importance of personalised healthcare and the value of endotype-driven assessment and management [133]. However, to date, both RCTs and real-world studies have largely examined the effects of pharmacological treatment at a population level. Thus, although treatment has been shown to have a statistically significant impact on symptoms, exacerbations and airflow obstruction, the scale of the effects at the group level are often limited, suggesting that not all patients may gain the same effect from treatment. Thus, as we enter an era of personalised medicine, there is a need to identify the individual patient factors that are associated with treatment response.

The recent shift towards a treatment approach guided by treatable disease characteristics, or traits [134], that is less dependent on conventional diagnostic labels, has highlighted a lack of studies that span both

TABLE 3 Author's appraisal of selected comparative effectiveness studies using RELEVANT 2.0 tool [121]

| Author and study name | Study design | Primary item score n out of 11 (%) | Secondary item score n out of 10 (%) |
|---|---|---|---|
| **Vestbo *et al.* [10] Salford Lung Study** | Pragmatic RCT | 10 (91%) | 8 (80%) |
| **Bosnic-Anticevich *et al.* [29]** | Historical matched cohort study | 11 (100%) | 8 (80%) |
| **Buhl *et al.* [26] DACCORD Study** | Prospective observational study | 10 (91%) | 8 (80%) |
| **Kardos *et al.* [27] DINO and DACOTA studies** | Prospective observational cohort studies | 10 (91%) | 10 (100%) |
| **Ocakli *et al.* [34]** | Cross-sectional observational study | 8 (73%) | 5 (50%) |
| **Zeiger *et al.* [38]** | Prospective observational study | 11 (100%) | 6 (60%) |

RCT: randomised controlled trial.

COPD and asthma across a broad range of severities. In order to provide a greater understanding of the value of a personalised healthcare approach in patients in clinical practice, there is a need for large-scale, inclusive observational studies with standardised outcome measures and a focus on patient-reported outcomes, physician assessments, airway physiology and blood and airway biomarkers across both primary and specialist care. The NOVEL observational longiTudinal studY (NOVELTY) study (NCT02760329) is one such study that aims to address this need [135]. NOVELTY is a global (19 countries), 3-year prospective, observational study of >12 000 patients with a diagnosis or suspected diagnosis of asthma and/or COPD that aims to describe patient characteristics, treatment patterns and burden of illness, and to identify the clinical phenotypes and molecular endotypes (based on biomarkers and/or clinical parameters) that are associated with differential outcomes for symptom burden, clinical evolution and healthcare utilisation over time. It is expected that the majority of patients enrolled in NOVELTY would not have been eligible for inclusion in most RCTs, therefore NOVELTY offers the prospect of investigating disease mechanisms and outcomes in a more clinically relevant population than that provided by a classical RCT.

## Conclusions

Real-world evidence is capable of providing valuable insights into disease mechanisms and management; however, due to the potential for producing large amounts of data and analyses compared with RCTs, it is vital that they are designed with clear research questions in mind. These research questions may demand different methodologies and, as such, will guide the type of study that is required. This will help to challenge perceptions that real-world evidence is solely for the evaluation of safety/epidemiology, and will demonstrate that they can also inform on patient outcomes if designed with clear research questions. Furthermore, due to the inclusion of a broader range of patients than RCTs, real-world studies require a much greater understanding of confounders and modifiers of effects compared with RCTs to aid interpretation of their findings.

Observational real-world studies are a vital component of research into obstructive lung disease, and well-designed observational studies can support pivotal RCTs and provide evidence that has the potential to influence clinical practice. Although observational studies are subject to specific challenges, with the aid of recently developed quality standard tools, these challenges can be factored into study design to produce high-quality results. In future, well-designed, real-world studies that include a broad range of patients (in terms of geographical location, care setting and severity level) across both asthma and COPD diagnoses will be instrumental in supporting a more personalised, endotype-driven approach to the assessment and management of patients with obstructive lung disease.

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