Randomised controlled trials in severe asthma: selection by phenotype or stereotype

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RCTs of biological therapies in severe asthma are poorly generalisable with most patients excluded by outmoded disease concepts despite possessing the targetable trait addressed by the treatment
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ABSTRACT Previous publications have highlighted the disparity between research trial populations and those in clinical practice, but it has not been established how this relates to randomised controlled trials (RCTs) of phenotype-targeted biological therapies in severe asthma.

Detailed characterisation data for 342 severe asthma patients within the Wessex Severe Asthma Cohort (WSAC) was compared against comprehensive trial eligibility criteria for published phase IIB and phase III RCTs evaluating biological therapies in severe asthma since 2000.

37 RCTs evaluating 20 biological therapies were identified. Only a median of 9.8% (range 3.5–17.5%) of severe asthma patients were found to be eligible for enrolment in the phase III trials. Stipulations for airflow obstruction, bronchodilator reversibility and smoking history excluded significant numbers of patients. A median of 78.9% (range 73.2–86.6%) of patients with severe eosinophilic asthma would have been excluded from participation in the phase III licensing trials of interleukin (IL)-5/IL-5R targeted therapies.

Despite including only well characterised and optimally treated severe asthmatics under specialist care within the WSAC study, the vast majority were excluded from trial participation by criteria designed to re-confirm diagnostic labels rather than by biomarker criteria that predict the characteristic addressed by the treatment.

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Introduction

Asthma affects over 300 million people worldwide with an estimated total annual cost in the UK approaching £5 billion [1, 2]. Whilst the majority of people with asthma can be treated effectively with inhaled corticosteroids (ICS) and bronchodilators, 5–10% with severe asthma suffer persistent symptoms, frequent exacerbations and an accelerated decline in lung function despite treatment [3]. Severe asthma is significantly more expensive with increased healthcare resource usage and high-cost medications accounting for much of this additional cost [4].

Cohort studies and cluster analyses have advanced our understanding of severe asthma, establishing it as a heterogeneous condition encompassing multiple phenotypes with underlying endotypes [5–9] defined by specific pathobiological pathways that underpin the manifestations of the disease. To address the significant unmet clinical need in severe asthma, there has been a focus since the turn of the millennium on developing biological therapies to target specific components of these inflammatory pathways (predominantly in those with Type-2 inflammation) [10]. These targeted interventions are recognised as an important step towards personalised medicine for patients with severe asthma. However, such treatments are expensive mandating that their use is rationalised by high-quality clinical evidence of efficacy and effectiveness, and the use of biomarkers to stratify patients and determine those most likely to benefit from treatment.

Recent expert commentary has proposed that less emphasis be placed on historical definitions of asthma, highlighting that most randomised controlled trials (RCTs) study populations that are poorly generalisable to clinical practice [11, 12], with a focus instead on "treatable traits" to identify clinical trial populations who are most likely to benefit from an intervention. Previous studies have shown that only 3.3–6% of patients with asthma fulfilled the eligibility criteria for the clinical trials upon which asthma guidelines are based [13, 14]. However, these studies did not focus on patients with severe asthma under specialist care or biological therapies targeting specific asthma phenotypes and thus it is unclear whether a similar impact on the generalisability of trial data exists.

To investigate this we have therefore aligned the data from a large well characterised cohort of severe asthma patients, the Wessex Severe Asthma Cohort (WSAC), with the clinical trial eligibility criteria of published RCTs assessing biological therapies in severe asthma. Additionally, we have compared the profile of the WSAC with published data from other severe asthma cohorts to evaluate how representative this cohort is of the broader severe asthma population, so that the implications of these findings can be fully appreciated.

Methods

Study design

The WSAC is an observational, cross-sectional study providing detailed characterisation of severe asthma patients recruited from specialist severe asthma clinics at Portsmouth and Southampton Hospitals between April 2009 and January 2014. Study participants had asthma, confirmed by a specialist in accordance with the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guidelines 2009, which remained poorly controlled with persisting symptoms and exacerbations despite treatment with high-dose ICS (or maintenance systemic corticosteroids), a long-acting β_2-agonist (LABA) and/or alternative controller medications (equivalent to step 4 or step 5 of the Global Initiative for Asthma (GINA) management guidelines for asthma 2017 [15]), as well as focused management of any co-morbid conditions (full inclusion criteria are included in the supplementary material).

Characterisation protocol

All participants underwent a detailed characterisation protocol including clinical, physiological and biological assessments (full details are included in the supplementary material). The study was funded by the UK Medical Research Council (MRC)/National Institute for Health Research (NIHR) Patient Research Cohorts Initiative and was conducted in accordance with the International Conference on Harmonisation and Good Clinical Practice standards and the ethical principles outlined in the Declaration of Helsinki. Independent ethics committee approval was obtained (MREC No. 09/H0502/37) and all participants provided written, informed consent prior to participation in the study.

Identification of trials and eligibility analysis

A systematic search was used to identify all phase IIB and phase III RCTs studying novel treatments in severe asthma between January 2000 and January 2018. Abstracts were reviewed and primary publications sought for relevant RCTs (the reference lists of these publications were also reviewed). Key eligibility criteria were extracted from primary publications, published trial protocols and clinical trial databases where available. Each patient from the WSAC was assessed against the eligibility criteria for each trial to determine the numbers that would have been deemed suitable for enrolment and key criteria which

excluded patients from trial participation were reviewed. Criteria were divided into diagnostic criteria (*e.g.* airflow obstruction and reversibility) and biomarker criteria (*e.g.* peripheral blood eosinophil count), with the latter used to identify a specific disease phenotype. Where relevant data was unavailable it was assumed patients remained eligible, with the exception of studies mandating sputum eosinophilia where failure of sputum production precluded enrolment. In addition, each patient was assessed against the National Institute for Health and Care Excellence (NICE) treatment recommendations for biological therapies currently licenced for use in asthma in the UK. The primary outcome was the proportion of patients eligible for each of the RCTs identified.

Role of the funding source
The UK MRC and NIHR provided joint funding for the study but did not contribute to its design or to collection, analysis or interpretation of the data.

Results

The WSAC enrolled 342 severe asthmatics, all of whom fulfilled the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2014 definition of severe asthma. A summary of the characteristics of this group is shown in table 1 and further details are included in the supplementary material. The severe asthma patients within the WSAC are demographically comparable to previous cohorts/registries, as detailed in the supplementary material.

37 RCTs, comprising 23 phase II and 14 phase III trials, assessing 20 novel therapies in over 15 000 patients with severe asthma were identified. Of these RCTs, 29 (78%) assessed treatments targeting the Type-2 "high" inflammatory pathway. The most frequent primary endpoint was a reduction in exacerbation frequency (71% of phase III trials).

Only a median of 9.8% (range 3.5–17.5%) of severe asthma patients within the WSAC would have been eligible for enrolment in the phase III trials of biological therapies in severe asthma. The proportion of patients within the WSAC who would have been suitable for enrolment in each RCT is shown in table 2. Whilst there is an increment in eligibility between phase II and phase III RCTs, overall suitability remains low.

Commonly used eligibility criteria and their impact on trial enrolment are highlighted in table 3. The requirements for persistent airflow obstruction and/or significant bronchodilator reversibility were key reasons for trial exclusion and when both criteria were required only 33.6% of severe asthma patients in the WSAC remained eligible. The cumulative effect of multiple eligibility criteria dramatically restricts eligibility for trial participation. However, the use of composite inclusion criteria, allowing bronchodilator reversibility, bronchial hyper-responsiveness and/or measures of variable airflow obstruction, modestly increases median eligibility from 7.6% (range 2.1–30.7%) to 15.8% (range 4.1–39.5%).

In table 2, eligibility is subdivided into asthma and biomarker criteria, which demonstrates that the majority of patients are excluded by non-phenotypic criteria. The percentage of patients with blood eosinophil counts of $\geqslant$300 cells·μL^{-1} who would have been eligible for enrolment in published phase III trials of IL-5 and IL-5R targeted therapies is illustrated in figure 1. Again this demonstrates that most are excluded by non-phenotypic criteria. A similar effect is seen with an eosinophilic population defined as $\geqslant$2% or $\geqslant$3% of sputum eosinophils, or by blood eosinophil counts of $\geqslant$150 cells·μL^{-1} (supplementary material). The median eligibility for RCTs assessing biological agents targeting Type-2 asthma (8.8%, range 2.1–26.9%) was lower than for non-Type-2 asthma (14%, range 5.3–39.5%) and comparative RCTs of novel non-biological therapies for severe asthma (33.9%, range 20.8–76.9%).

Within the WSAC, 26% of severe asthmatics were current smokers or ex-smokers with a smoking history of $\geqslant$10 pack-years. Of those patients who successfully produced sputum (59 out of 90; 62%) or had a peripheral blood count (81 out of 90; 90%), 56% had a sputum eosinophil count of $\geqslant$2% and/or a peripheral blood eosinophil count of $\geqslant$300 cells·μL^{-1} but were not eligible for enrolment in most trials targeting Type-2 "high" disease due to their smoking status. The impact of smoking on Type-2 biomarker status in the WSAC is shown in table 4.

That less than 50% of the severe asthmatics in the WSAC who fulfilled the NICE recommendations for treatment with mepolizumab and reslizumab would have been eligible for inclusion in the phase III trials of these therapies (mepolizumab 45.3%; reslizumab 33.9%) is demonstrated in figure 2.

Discussion

The WSAC was established with the aim of evaluating real-world severe asthma patients and is comparable to the severe asthma populations described in previously published cohorts and registries [7, 16–19], from which cluster analyses have identified the currently recognised asthma phenotypes. Despite including only well characterised and optimally treated severe asthmatics under specialist care, the

TABLE 1 Wessex Severe Asthma Cohort (WSAC) characteristics summary (n=342)

Characteristic	Result
Patient demographics	
Age years	49.4±13.6
Female	67.5
BMI kg·m^{-2}	29.7 (25.6–35.6)
BMI >30 kg·m^{-2}	48.2
Smoking status	
Never smoker	55
Ex-smoker	39.2
Current smoker	5.8
Ex-smoker pack-years	10 (4.4–22.5)
Current smoker pack-years	20 (8.4–35)
Asthma history	
Asthma duration years	26±17
ICS dose BDP equivalent µg·day^{-1}	2369±1149
LABA	95.8
LTRA	67.6
LAMA	31.3
Theophylline	26.2
Maintenance OCS	34.2
Prednisolone equivalent dose mg	15.9±12
Asthma control	
Rescue OCS courses in the previous year	2 (1–4)
⩾1 hospital admissions in the previous year	50.3
ACQ6 score	2.74±1.24
ACQ6 score >1.5	82.5
Previous intensive care admission for asthma	18.1
AQLQ score	4.09±1.26
Comorbidities	
Gastro-oesophageal reflux disease	48.5
PPI use	45.5
Rhinosinusitis	72.5
Rhinosinusitis treatment	72.8
Nasal polyps	14
Physiological measures	
Pre-brochodilator FEV_1 % predicted	69.6±24.9
FEV_1 reversibility % from baseline	13.3 (5.2–26.4)
Reversibility ⩾12%[#]	43.3
Atopic status	
Atopic[¶]	72.4
Measures of inflammation	
$F_{ENO_{50}}$ ppb	20.7 (12.7–41)
$F_{ENO_{50}}$ ⩾50 ppb	20.7
Sputum inflammatory phenotype	
⩾3% eosinophilic	41.1
⩾60% neutrophilic	37.3
Mixed granulocytic	10.5
Paucigranulocytic	32.1
Blood eosinophil count ×10^9 per L	0.2 (0.1–0.5)
Blood eosinophil count ⩾0.3	49
ATS/ERS severe asthma criteria 2014 [3]	
GINA step 4/5 treatment	100
ACQ6 score >1.5[+]	82.5
⩾2 OCS bursts in the previous year[+]	74
⩾1 hospital admission in the previous year[+]	50.3
Persistent airflow limitation[+]	66.5

Data are presented as %, mean±SD or median (interquartile range). BMI: body mass index; ICS: inhaled corticosteroids; BDP: beclometasone dipropionate; LABA: long-acting β_2-agonist; LTRA: leukotriene receptor antagonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroids; ACQ6: asthma control questionnaire 6; AQLQ: asthma quality of life questionnaire; PPI: proton pump inhibitor; FEV_1: forced expiratory volume in 1 s; $F_{ENO_{50}}$: exhaled nitric oxide fraction at 50 mL·s^{-1} flow rate; ATS: American Thoracic Society; ERS: European Respiratory Society; GINA: Global Initiative for Asthma. [#]: reversibility testing was performed 15 min after administration of 2.5 mg nebulised salbutamol; [¶]: atopic was defined as one or more positive skin prick tests; [+]: 100% of patients in the WSAC meet one or more of the four major "poor control" criteria.

TABLE 2 Summary of Wessex Severe Asthma Cohort (WSAC) trial exclusions[#]

Target	Drug	First Author[¶]	Year	Phase	WSAC eligibility %		
					Biomarker criteria	Asthma criteria	Overall
IgE	Omalizumab	Holgate	2004	III	36.84	12.57	3.51
	Omalizumab	Humbert	2005	II	36.84	11.70	4.09
	Omalizumab	Hanania	2011	III	36.84	18.42	6.14
IL-5	Mepolizumab	Haldar	2009	II	25.15	23.10	7.89
	Mepolizumab	Nair	2009	II	25.15	23.10	5.56
	Mepolizumab	Pavord	2012	III	57.31	23.10	17.54
	Mepolizumab	Bel	2014	III	69.59	8.77	4.09
	Mepolizumab	Ortega	2014	III	69.59	23.98	15.79
	Mepolizumab	Chupp	2017	III	69.59	23.39	14.91
	Reslizumab	Castro	2011	II	25.15	22.81	4.68
	Reslizumab	Castro	2015	III	45.32	23.68	8.77
	Reslizumab	Castro	2015	III	45.32	23.68	8.77
	Reslizumab	Bjermer	2016	III	45.32	29.24	10.82
	Reslizumab	Corren	2016	III	100.00	15.50	15.50
	Benralizumab	Bleeker	2016	III	100.00	11.11	11.11
	Benralizumab	FitzGerald	2016	III	100.00	11.11	11.11
IL-13	Tralokinumab	Piper	2013	II	100.00	26.90	26.90
	Tralokinumab	Brightling	2015	II	100.00	11.40	11.40
	Lebrikizumab	Corren	2011	II	100.00	6.14	6.14
	Lebrikizumab	Hanania	2016	III	100.00	7.60	7.60
	Lebrikizumab	Hanania	2016	III	100.00	7.60	7.60
	GSK679586	De Boever	2014	II	100.00	18.42	18.42
IL-4Rα	AMG317	Corren	2010	II	73.68	3.80	3.51
	Dupilumab	Wenzel	2013	II	36.55	2.92	2.05
	Dupilumab	Wenzel	2016	II	100.00	10.53	10.53
	Pitrakinra	Slager	2012	II	100.00	23.39	23.39
IL-4/5	Suplatast	Tamaoki	2000	II	100.00	6.43	6.43
DP2	Fevipiprant	Gonem	2016	II	27.19	59.65	16.67
IL-2Rα	Daclizumab	Busse	2008	II	73.68	6.73	5.26
TSLP	Tezepelumab	Corren	2017	II	100.00	6.43	6.43
c-Kit/PDGF	Masitinib	Humbert	2009	II	99.12	5.56	5.26
CXCR2	Navarixin	Nair	2012	II	36.84	55.56	19.88
	AZD5069	O'Byrne	2016	II	71.93	37.72	25.15
IL17RA	Brodalumab	Busse	2013	II	100.00	6.73	6.73
TNF-α	Etanercept	Morjaria	2008	II	100.00	39.47	39.47
	Etanercept	Holgate	2011	II	100.00	8.19	8.19
	Golimumab	Wenzel	2009	II	100.00	30.70	30.70
Non-biological	BT	Castro	2010	III	100.00	26.32	26.32
	Azithromycin	Brusselle	2013	III	73.98	31.58	20.76
	Azithromycin	Gibson	2017	III	100.00	76.90	76.90
	TLA	Storrar	2017	III	73.68	53.80	41.52

IL: interleukin; DP2: prostaglandin D_2 receptor 2; TSLP: thymic stromal lymphopoietin; c-kit: proto-oncogene c-Kit; PDGF: platelet-derived growth factor; CXCR2: C-X-C motif chemokine receptor 2; TNF-α: tumour necrosis factor-α; BT: bronchial thermoplasty; TLA: temperature-controlled laminar airflow. [#]: full details are available in the supplementary material; [¶]: full references are available in the supplementary material.

vast majority of patients in the WSAC (90.2%; range 82.5–96.5%) would have been excluded from the landmark phase III trials of biological therapies published to date.

Severe asthma is a heterogeneous condition and biological therapies are only likely to benefit subsets of the population. It would seem reasonable to assume that the majority of patients with poorly-controlled severe eosinophilic asthma (despite high-dose inhaled steroids) should have been eligible for inclusion in RCTs of therapies targeting inflammatory mediators of the Type-2 asthma pathway. However, a median of only 21.1% (range 13.4–26.8%) of patients with severe eosinophilic asthma in the WSAC (as defined by a blood eosinophil count of $\geqslant$300 cells·μL^{-1}) would have been eligible for the phase III trials of these therapies.

TABLE 3 The impact of commonly used eligibility criteria on Wessex Severe Asthma Cohort (WSAC) eligibility

Eligibility criteria	Trials n	Criteria variants n	Specific criteria examples	Trials n	WSAC eligibility %
Airflow obstruction	29	12	FEV_1 (pre-bronchodilator) ⩽80%	23	66.7
			FEV_1 (pre-bronchodilator) ⩾40%	11	87.72
			FEV_1 (pre-bronchodilator) 40–80%	9	54.4
Bronchodilator reversibility	35[#]	6	⩾12% increase in FEV_1	32	43.3
			⩾12% and 200 mL increase in FEV_1	16	38.9
Exacerbation frequency	18	5	⩾2 in the last 12 months	11	74
			⩾2 OCS or ⩾1 hospital	3	79.5
ACQ	21[¶]	6	ACQ7 ⩾1.5	5	86
			ACQ6 ⩾1.5	8	86.6
Smoking status	35	7	Current smokers excluded	34	83.3
			<10 pack-years	24	79.5
ICS dose (BDP equivalent)	35	9	⩾1000 μg·day^{-1}	16	93.9
			⩾2000 μg·day^{-1}	3	69.6
OCS use	37	5	No	11	65.8
			⩽10 mg·day^{-1}	6	84.2

FEV_1: forced expiratory volume in 1 s; OCS: oral corticosteroids; ACQ: asthma control questionnaire; ICS: inhaled corticosteroids; BDP: beclometasone dipropionate; [#]: 14 trials used a composite criterion allowing bronchodilator reversibility or bronchial hyper-responsiveness and in some cases other measures of variable airflow obstruction (*e.g.* diurnal peak expiratory flow rate variability); [¶]: one trial used the asthma control test.

There is significant heterogeneity in the eligibility criteria used between trials despite the aim of reconfirming a diagnosis of asthma in a similar target population. For example, whilst 30 of the 37 RCTs required demonstrable airflow obstruction, 12 unique criteria were used to define this. Whilst some studies adopted pragmatic composite eligibility criteria to broaden inclusion, many still required specific evidence

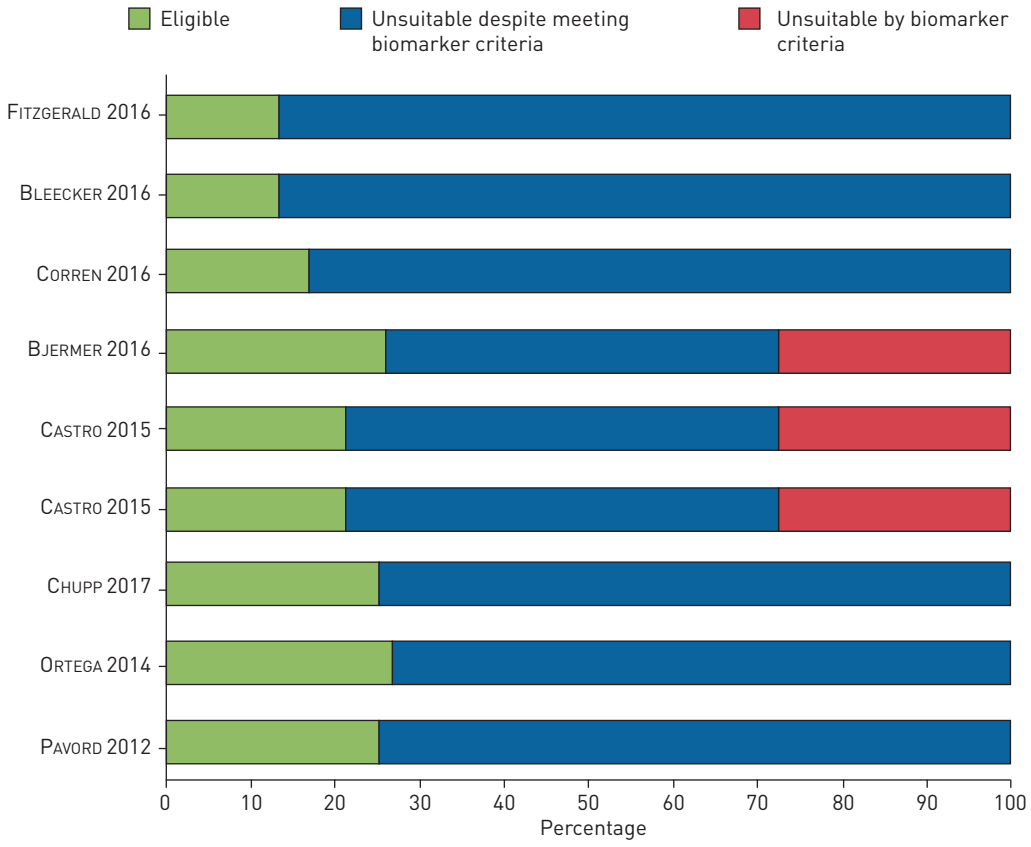

FIGURE 1 Trial eligibility for phase III interleukin (IL)-5 targeted treatments in severe asthmatics with a blood eosinophil count of ⩾300 cells·μL^{-1}

TABLE 4 The impact of smoking on Type-2 biomarker status in the Wessex Severe Asthma Cohort (WSAC)

Smoking status	Subjects	Sputum tests	Blood tests	Biomarker status				
				Sputum eosinophils		Blood eosinophils		
				⩾2%	⩾3%	⩾150 per µL	⩾300 per µL	⩾400 per µL
Never smoker	188	107 (56.9)	156 (83.0)	55 (51.4)	51 (47.7)	98 (62.8)	79 (50.7)	60 (38.5)
Ex-smoker <10 pack-years	64	43 (67.2)	53 (82.8)	13 (30.2)	12 (27.9)	36 (67.9)	29 (54.7)	19 (35.8)
Ex-smoker ⩾10 pack-years	70	43 (61.4)	64 (91.4)	20 (46.5)	18 (41.9)	45 (70.3)	30 (46.9)	21 (32.8)
Current smoker	20	16 (80)	17 (85)	5 (31.3)	5 (31.3)	7 (41.2)	4 (23.5)	3 (17.6)

Data are presented as n or n (%).

of bronchodilator reversibility and/or persistent airflow limitation, which dramatically reduced patient eligibility. In the WSAC, of those patients with a sputum eosinophil count of ⩾3%, an asthma control questionnaire (ACQ) score greater than 1.5 and at least one severe exacerbation in the past year, 23% had no evidence of persistent airflow limitation, 56% did not have 12% bronchodilator reversibility and 61% were excluded when both features were required.

In a similar fashion to other cohorts, 26% of the severe asthmatics in the WSAC were current smokers (5.8%) or ex-smokers with a smoking history of ⩾10 pack-years (20.5%). Whilst it is reported that asthma in smokers is generally associated with non-eosinophilic inflammation [20], a significant proportion in the WSAC did have demonstrable airway eosinophilia. It is recognised that asthmatics who smoke have impaired responsiveness to corticosteroids and suffer more frequent exacerbations and an accelerated rate of lung function decline [21, 22]. Arbitrary exclusion of these patients from trials has led to a paucity of evidence upon which to base treatment decisions for them. It is also important to reflect that other factors impacting upon airway biology, including obesity, persisting allergen exposure and bacterial dysbiosis, are not commonly included within trial eligibility criteria, raising a question of equity.

RCTs of Type-2 targeted therapies excluded significantly more participants on the basis of diagnostic criteria than those evaluating non-Type-2 and non-biological therapies. This suggests hyper-selection within this population, further limiting generalisability of the results. Licensing body and healthcare funder recommendations extrapolate from RCTs which we have demonstrated to be poorly representative of real-life severe asthma populations. The disparity between NICE treatment recommendations and the trial populations is highlighted in figure 2. The residual uncertainty this has created as to the benefit of treatment for many patients has led to a reliance on treatment trials. Avoiding eligibility criteria that are

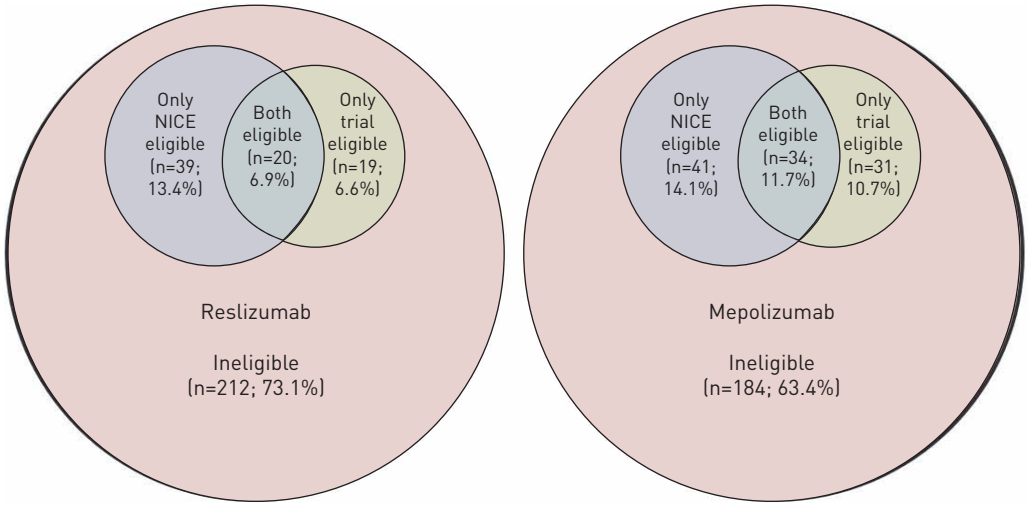

FIGURE 2 A comparison of National Institute for Health and Care Excellence (NICE) treatment recommendations and phase III trial eligibility. All phase III trials were included using eligibility criteria from NICE technology appraisal guidance TA431 (January 2017) and TA479 (October 2017). For full criteria see the supplementary material.

not relevant to the biological trait targeted would allow for a more inclusive trial population that is better able to be generalised to the subsequent treatment population.

Regulatory authorities have a major influence over the design of RCTs required for product licencing. The European Medicines Agency guidelines for asthma trials specify "the aim should be to study a homogeneous population of patients with asthma" and recommend evidence of reversible airflow obstruction for a secure diagnosis of asthma, substantially limiting trial eligibility [23]. Phase IV pragmatic and non-randomised trials have proved crucial in demonstrating treatment efficacy in those patients excluded from licencing trials [24–26]; however, this creates a significant delay in the generation of evidence for many severe asthma patients and carries the risk of inflating the impact, as real-world evidence is not placebo-controlled. Pragmatic phase III RCTs which better reflect real-world populations and clinical practice may improve external validity and equity of access [27]; however, this will require engagement between clinicians, licencing authorities, funding bodies and the pharmaceutical industry.

Our findings show that RCTs in severe asthma lack external validity, with the majority of patients excluded by criteria designed to confirm arbitrary diagnostic labels rather than by biomarker criteria that predict the characteristic or trait addressed by the treatment [11, 12]. Failure to adopt an exclusively phenotypic approach to trial inclusion will perpetuate the limited generalisability of evidence on effectiveness and health economics used by regulatory bodies. This risks the missing of opportunities for the application of novel therapies and also the propagation of the vast unmet need in severe asthma.

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