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Treatable Trait Guided Asthma Management: A Feasibility Study

James Fingleton[1] | Rob McLachlan[1,2] | Jenny Sparks[2] | Richard Beasley[2] | Alvar Agustí[3] | Peter G. Gibson[4] | Ian D. Pavord[5] | Jo Hardy[2] | Mark Weatherall[6] | Allie Eathorne[2] | Vanessa M. McDonald[4] | the Treatable Traits Study Group

[1]Te Whatu Ora – Capital, Coast and Hutt Valley, Wellington, New Zealand | [2]Medical Research Institute of New Zealand, Wellington, New Zealand | [3]University of Barcelona, Clinic Barcelona, IDIBAPS, CIBERES, Barcelona, Spain | [4]College of Health and Wellbeing, University of Newcastle, Newcastle, New South Wales, Australia | [5]NIHR Respiratory BRC, University of Oxford, Oxford, UK | [6]University of Otago Wellington, Wellington, New Zealand

Correspondence: James Fingleton (james.fingleton@ccdhb.org.nz)

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ABSTRACT

Background and Objectives: Treatable trait-based personalised medicine improves outcomes in severe asthma clinics. We assessed the feasibility of a randomised controlled trial (RCT) of protocolised treatable trait-guided asthma management in patients not under a severe asthma clinic.

Methods: Ten week single-group cohort study. Participants had a doctor's diagnosis of asthma, Asthma Control Questionnaire-5 (ACQ-5) score > 1, and ≥ 1 exacerbation in the last year. Intervention: biomarker-guided asthma medication according to a protocolised algorithm, targeting traits of type-2 inflammation and airflow obstruction. Feasibility outcomes: recruitment rates, acceptability of intervention, willingness to enrol in an RCT, need for 'extended' trait assessment after 10 weeks, and estimation of trait prevalence.

Results: Recruitment ceased with 29/50 participants after 14 months due to difficulties associated with COVID-19. Recruitment rate: 29/118 (25%) of those invited to participate (95% CI 17 to 33). 24/26 (92%) participants found the intervention acceptable and were willing to participate in a future study. After 10 weeks, 65% remained not well controlled (ACQ-5 > 1) and would have required the 'extended' assessment. Participants had a mean (SD) 4.8 (2.3) of 13 traits assessed.

ACQ-5 improved during the study by −1.0 (0.3 to 1.8) units, and post-bronchodilator airflow limitation reduced from 59% of participants to 35%. 12/29 (41%) participants received continuous oral corticosteroids at some point during the study.

Conclusion: Protocolised treatable trait management was acceptable to participants, associated with significant clinical benefit, and a full RCT appears feasible. Targeting type-2 inflammation and airflow obstruction was insufficient to control asthma in the majority of patients, despite marked systemic corticosteroid exposure.

Trial Registration: ACTRN12620000935932

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Summary

- A protocolised treatable trait asthma management program was associated with significant clinical benefit, paving the way towards a randomised controlled trial.
- Importantly, we observed that targeting type-2 inflammation and airflow obstruction only was insufficient to control asthma in the majority of patients, despite significant systemic corticosteroid exposure.

1 | Introduction

The concept of treatable traits in airways disease recognises that chronic airways diseases such as asthma and chronic obstructive pulmonary disease (COPD) can be complex syndromes with multiple mechanistic drivers. These may require individualised investigation and treatment to take account of different patterns of inflammation and multiple overlapping conditions and comorbidities [1–3]. Treatable traits are patient characteristics that can be identified by clinical, physiological, or biological markers, or other investigations; are treatment responsive, and have clinical relevance. They represent a pathway to precision medicine. This approach can potentially improve clinical outcomes for patients by targeting specific treatments to optimise efficacy and minimise unnecessary adverse effects for those less likely to respond to specific treatments [4].

This approach is widely used internationally in tertiary hospital severe asthma clinics, although usually called systematic or multidimensional assessment, and is associated with improvements in asthma control, better quality of life, and reduced severe exacerbations [5]. However, there is limited randomised controlled trial (RCT) evidence for the treatable traits approach in patients with less severe asthma, and no information on the feasibility of this approach outside tertiary referral clinics. Better evidence is needed to determine if a protocol-based treatable trait approach to asthma management is superior to guideline-directed care in those with moderate asthma.

The aim of the study reported here was to address feasibility issues associated with the design of an RCT of a protocol-based biomarker-guided treatable trait approach to asthma for patients whose asthma was not managed within a severe asthma clinic. The five specific feasibility issues were: estimation of recruitment rate, acceptability of the intervention, willingness to enrol in a full RCT, need for 'extended' trait assessment after 10 weeks, and trait prevalence.

2 | Methods

A 10-week single group cohort study.

2.1 | Participants

Participants were recruited at two sites: the Medical Research Institute of New Zealand facility at Wellington Regional Hospital, Wellington, New Zealand, and the Hunter Medical Research Institute and John Hunter Hospital, Newcastle, Australia.

Participants had self-reported doctor-diagnosed asthma with at least one severe exacerbation in the last year. In addition, participants had 'not well-controlled' asthma, with an Asthma Control Questionnaire—5 (ACQ-5) score > 1, despite receiving treatment at Step 2 or above, and did not meet the American Thoracic Society/European Respiratory Society (ATS/ERS) definition of severe asthma [6]. Patients already under the care of a severe asthma clinic or who were receiving high-dose inhaled corticosteroids, biological therapy, or maintenance oral corticosteroids were not recruited. Full details of inclusion and exclusion are shown in the protocol in the Supporting Information.

Potential participants were identified from existing research institute databases, asthma clinicians, GP mail-outs, and direct advertising (including via social media). This study was performed in accordance with the Declaration of Helsinki. This human study was approved by the Central Health and Disability Ethics Committee—approval: 20/CEN/33. The trial was prospectively registered on the Australian New Zealand Clinical Trials Registry. The study's clinical trial registration number is ACTRN12620000935932. Participant registration took place from September 2020 to December 2021. All adult participants provided written informed consent to participate in this study. There were no significant changes to methods or eligibility after trial commencement.

2.2 | Cohort Study

Participants attended an initial screening visit to determine eligibility. If eligible, participants were enrolled and had three visits over a 10-week period (Figure 1). A full schedule of study procedures and detailed methods is shown in the protocol (Supporting Information) and is described briefly here.

At the first visit, demographic descriptors, current medication, past medical history, and tobacco smoking history were recorded using a standardised format. Participants also completed a set of patient-reported outcome measures (PROMS), spirometry including testing for reversibility, and biomarker testing. Current smoking status was confirmed using urinary cotinine or exhaled carbon monoxide testing at each visit.

2.2.1 | PROMs

These were paper versions of the ACQ-5 [7], the standardised version of the Asthma Quality of Life Questionnaire (AQLQ(S)) [8], and the Saint George Respiratory Questionnaire (SGRQ) [9].

2.2.2 | Exhaled Nitric Oxide (FeNO)

FeNO was measured on a NiOX Vero in accordance with ATS guidelines [10]. The mean of three repeatable measurements was used.

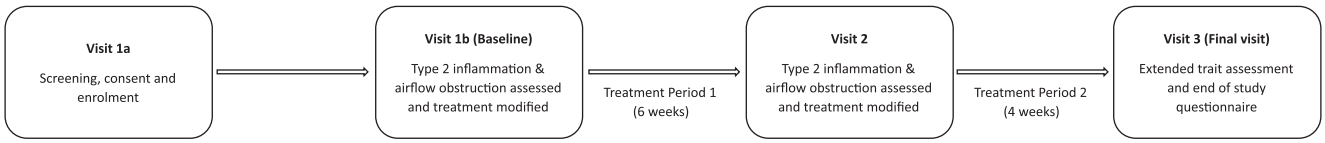

FIGURE 1 | Study schematic.

2.2.3 | Spirometry

Spirometry and reversibility were performed in accordance with ATS/ERS guidelines using a hand-held spirometer [11, 12].

2.2.4 | Laboratory Testing

Venous blood was drawn for blood eosinophil count, total white cell count, and C-reactive protein, with testing performed at the local accredited laboratory.

2.2.5 | Inhaler Adherence and Technique

Inhaler technique was assessed at study entry using the participants' usual ICS-containing inhaler. Turbuhaler technique education was provided at initial medication dispensing and repeated at repeat dispensing.

2.3 | Protocol-Based Treatment

At each visit, participants were assessed for the presence of two traits, type 2 airway inflammation and airflow obstruction. The protocol for medication adjustment is shown in Table 1. Medication was adjusted according to biomarkers as per Table 1c and then participants had a 6-week period of treatment (treatment period 1), after which they returned for repeat assessment of type 2 inflammation and airflow obstruction. Treatment was again adjusted according to Table 1c and participants had a 4-week period of treatment (treatment period 2), after which they returned for a final visit. At the final visit, an extended trait assessment was performed, and no medication was dispensed.

2.3.1 | Extended Trait Assessment

At a final visit, participants were also assessed for the presence of an extended list of traits as indicated by relevant trait identification markers (TIMs), shown in Table 2. This was to estimate the prevalence of these traits, which would be addressed in a future RCT if participants were not controlled after 10 weeks of biomarker-guided treatment of airway inflammation and airflow obstruction. This would allow the intended RCT to compare 3 interventions: usual care, two-trait, and 'extended' trait-based asthma management. As this extended list of traits was only assessed at the final study visit, these traits were not treated during this cohort study. At study completion, participants were reviewed by a respiratory specialist, and they and their primary care practitioner were informed of their study results. Appropriate management and/or referral to secondary care was recommended as clinically appropriate on an individual basis.

2.3.2 | End of Study Questionnaire

At the final visit participants completed an end of study questionnaire (see Supporting Information) with 2 statements, both answered on a 5-point Likert scale from 'strongly disagree' to 'strongly agree'. The first statement was 'I found having my medication adjusted according to my test results acceptable' and the second was 'I would be willing to take part in a study comparing usual care from my GP to "treatable trait-based asthma management"'.

2.4 | Feasibility Aims

1. Estimation of recruitment rate, defined as the proportion of those approached who participated in the cohort study.
2. Estimation of the proportion of participants who find the intervention acceptable, defined as those who agreed or strongly agreed with the statement 'I found having my medication adjusted according to my test results acceptable'.
3. Estimation of the proportion of participants who would be willing to be randomised in a trial comparing guideline directed care with management according to a treatable trait-based management algorithm, defined as those who agreed or strongly agreed with the statement 'I would be willing to take part in a study comparing usual care from my GP to "treatable trait-based asthma management"'
4. Estimation of the proportion of participants requiring the extended assessment protocol at the final visit, defined as the proportion of participants with either an ACQ-5 $\geq$ 1 at the final visit or an exacerbation between the first and final visits.
5. Estimation of the proportion of participants with each trait identified during the extended assessment.

2.5 | Sample Size

The sample size calculation for the feasibility study considered the proportion of those approached for the feasibility study who agree to participate and the proportion of those who participated in the feasibility study that stated they would agree to enter a RCT. We anticipated that 50% of those approached for the feasibility study would agree to participate in this, and that in turn 80% of those who participated in the feasibility study would agree to participate in a RCT; for a total potential recruitment rate of 40% of those who are approached. If this combined proportion was less than 25%,

TABLE 1 | Corticosteroid and bronchodilator adjustment algorithms with biomarker cut-points.

(a) Type 2 inflammation trait: Corticosteroid dosing adjustment algorithm

Biomarker results	Asthma control	Interpretation	Treatment change
Either FeNO or blood Eos or both are high	ACQ score ≥ 1	Strong evidence of T2 inflammation and not well controlled asthma (ACQ ≥ 1)	Increase corticosteroid treatment by one level
Either FeNO or blood Eos or both are high	ACQ score < 1	Strong evidence of T2 inflammation and well controlled asthma (ACQ < 1)	Increase corticosteroid treatment by one level up until level 3. Do not escalate above level 3[a]
At least one of FeNO and blood Eos are in the intermediate range and neither are high	ACQ ≥ 1	Intermediate evidence of T2 inflammation and not well-controlled asthma (ACQ ≥ 1)	Increase corticosteroid treatment by one level
At least one of FeNO and blood Eos are in the intermediate range and neither are high	ACQ < 1	Intermediate evidence of T2 inflammation and well controlled asthma (ACQ < 1)	No change to corticosteroid treatment
Both FeNO and blood EOS are low	Any ACQ score	No evidence of T2 inflammation	No change to corticosteroid treatment

(b) Biomarker cut-points

	Blood eosinophils ($\times 10^9$)	FeNO (ppb)	
		Non-smoker	Current smoker
High	≥ 0.3	≥ 40	≥ 28
Intermediate	≥ 0.15 and < 0.3	≥ 20 and < 40	≥ 14 and < 28
Low	< 0.15	< 20	< 14

(c) Airflow limitation trait: Bronchodilator algorithm

FEV_1:FVC ratio	Treatment change
If not on regular LABA	
Pre-bronchodilator/on-treatment FEV_1:FVC ≥ LLN	No change to bronchodilator treatment
Pre-bronchodilator/on-treatment FEV_1:FVC < LLN	Start regular long-acting beta-agonist by stepping up from as-needed to maintenance and reliever therapy
If on regular LABA	
Post-bronchodilator/on-treatment FEV_1:FVC ≥ LLN	No change to bronchodilator treatment
Post-bronchodilator/on-treatment FEV_1:FVC < LLN	Add Tiotropium Respimat 2.5 μg two inhalations once daily in addition to treatment as per Type 2 algorithm

(d) Type 2 inflammation trait: Corticosteroid treatment levels

Level		Daily FP dose equivalent
1	No regular ICS Budesonide/formoterol 200/6 Turbuhaler one inhalation as needed[b]	0 mcg
2	Budesonide/formoterol 200/6 Turbuhaler two inhalations twice daily and one as-needed[b]	At least 500 mcg (exact dose dependent on as-needed use)
3	Budesonide/formoterol 200/6 Turbuhaler two inhalations twice daily and one as-needed[b] *plus* Budesonide 200 mcg Turbuhaler two inhalations twice daily	At least 1000 mcg (exact dose dependent on as-needed use)

(Continues)

TABLE 1 | (Continued)

(d) Type 2 inflammation trait: Corticosteroid treatment levels		
Level		**Daily FP dose equivalent**
4	Budesonide/formoterol 200/6 Turbuhaler two inhalations twice daily and one as-needed[b] *plus* Budesonide 200 mcg Turbuhaler two inhalations twice daily *plus* Oral prednisone 10 mg daily	At least 1000 mcg (exact dose dependent on as-needed use) plus oral steroid
5	Budesonide/formoterol 200/6 Turbuhaler two inhalations twice daily and one as-needed[b] *plus* Budesonide 200 mcg Turbuhaler two inhalations twice daily *plus* Oral prednisone 20 mg daily	At least 1000 mcg (exact dose dependent on as-needed use) plus oral steroid

[a]Corticosteroid treatment levels described in Table 1d.
[b]Maximum total doses of budesonide/formoterol 12 per day. All participants received an asthma management plan recommending same-day medical review if requiring 8 or more doses of budesonide/formoterol in a day (combined total of maintenance and reliever doses) and presentation to an Emergency Department if reaching 12 doses.

then a RCT would need either a longer duration or more centres anticipated based on our knowledge of local patient numbers.

A sample size for potential recruitment of 100 has about 90% power to rule out a lower confidence bound for the recruitment proportion of less than 25%. We hoped to recruit 50 participants into the feasibility study at two sites to give a 95% CI for a proportion of plus or minus 15% for those that might be willing to join in an RCT. In the event, as described below, although one recruitment site was able to recruit 25 participants, the other site could not because of COVID-related restrictions.

2.6 | Statistical Analysis

Continuous data are summarised by mean and standard deviation (SD), median and inter-quartile range (IQR), and minimum to maximum. Categorical and ordinal data are summarised by counts and proportions expressed as percentages. Proportions and their confidence intervals are estimated by the exact technique. The difference in continuous variables at the first and last visit is analysed by paired t-test.

We also conducted an exploratory descriptive analysis of treatment administered and treatment response as measured by PROMs and FEV_1. A biomarker and responder analysis examined the change in biomarkers during the study and associations between baseline biomarker status and treatment response.

On the boxplots, the horizontal lines represent the median and 25th and 75th percentiles; the circle is the mean, and the whiskers extend to the minimum and maximum. Alluvial plots are used to show the flow of participants over time by changes in corticosteroid treatment level and composite biomarker status. The nodes represent level/status at the specified time point, and the change in level/status is represented by the flow.

SAS version 9.4 and R version 4.0.4 were used.

3 | Results

3.1 | Participant Flow

Between 21/09/2020 and 07/12/2021, 29 participants were recruited. Recruitment ceased after 14 months due to difficulties associated with COVID-19. The planned sample size of 25 per site was reached in Wellington, NZ, but regional lockdowns prevented recruitment in Newcastle, Australia, and recruitment was terminated after 4 of the planned 25 participants were enrolled in Australia.

Participant flow through the study is shown in Figure 2. Baseline participant data is shown in Table 3.

3.1.1 | Feasibility Aims

Pre-screening contact was made with 356 people, of whom 178 were excluded for not meeting exclusion criteria and 60 declined for other reasons. One hundred and eighteen people were invited to participate and 42/118 (35%) participants consented to participate. 29/42 met study inclusion criteria and were enrolled in the study, giving a recruitment rate of 69% (95% CI 53 to 82) of those screened, 25% (17 to 33) of those invited to participate and 8% (6 to 11) of those initially contacted.

Of the 29 participants enrolled in the study, 21/29 (72%) completed all three visits, and 26/29 completed the end-of-study questionnaire. Most, 24/26 (92%) found the intervention acceptable, and 24/26 (92%) were willing to be randomised in a future study. Almost two thirds, 17/26 (65%), remained not well controlled, with an ACQ-5 > 1 after 10 weeks. Estimated trait prevalence at the final visit is shown in Table 4. At study completion, participants had a mean (SD) 4.8 (2.3) from 13 traits assessed.

3.1.2 | PROMs

For participants in the cohort study, there were improvements in ACQ-5, SGRQ, AQLQ(S) and FEV_1. ACQ improved from

TABLE 2 | Trait identification markers.

Trait	Trait identification marker
Smoking	Urinary cotinine OR Exhaled breath carbon monoxide
Airway pathogen colonisation	Presence of bacterial pathogen via sputum culture
Frequent chest infection	≥2 respiratory-related antibiotic courses in 12 months
Rhinitis/Sinusitis	Sinonasal questionnaire score ≥1
Dysfunctional breathing	Nijmegen questionnaire total score ≥23
Vocal cord dysfunction/inducible Laryngeal obstruction	Pittsburgh Vocal Cord Dysfunction Index score ≥4
Depression	Hospital Anxiety and Depression Score (HADS), depression domain score ≥8
Anxiety	HADS anxiety domain score ≥8
Suboptimal adherence	<80% adherence to combination ICS-LABA, based on number of doses administered versus expected as estimated using dose counter recordings taken at visit 2 and 3
Systemic inflammation	Elevation of at least two systemic inflammatory markers on more than one occasion, high sensitivity CRP >3 mg/L, and WCC $>9\times10^9$/L
Occupational exposure	Systematic exposure history

Abbreviations: CRP, C-reactive protein; ICS-LABA, combined inhaled corticosteroid and long-acting beta-agonist; WCC, white cell count.

mean (SD) 2.7 (1.1) at the first visit to 1.6 (1.4) at the final visit; difference −1.0 (95% Confidence Interval: 0.3 to 1.8, $p=0.007$) units. SGRQ improved from 50.1 (16.0) to 34.6 (22.3); difference −15.1 units (95% CI: −21.1 to −9.2, $p<0.0001$). AQLQ(S) improved from 4.5 (1.2) to 5.5 (1.3); difference +1.0 units (95% CI: 0.5 to 1.5, $p=0.001$). FEV_1 improved from 2.6 (1)L to 3.1 (0.9)L, difference +0.4 L (95% CI: 0.2 to 0.6, $p=0.0003$) (Figure 3). Post-bronchodilator airflow obstruction reduced from 17/29 (59%) of participants at study commencement to 8/23 (35%) at the final visit.

3.1.3 | Treatment Allocation During the Study

Corticosteroid treatment allocation is shown in Table 5 and the Alluvial plot in Figure 4. During the cohort study period, there were 12/29 (41%) participants who received continuous oral corticosteroids in one or both treatment periods. Of these, 9 had a maximum prednisone dose of 10 mg per day, and 3 had a maximum dose of 20 mg per day. The 20 mg dose was administered for a maximum of 4 weeks. At study completion, participants were reviewed by a respiratory specialist, and they and their primary care practitioner were informed of their study results. Appropriate management and/or referral to secondary care was recommended as clinically appropriate on an individual basis. No participant continued on oral corticosteroids after their final visit.

Long-acting muscarinic antagonists were allocated to 12 participants at some point in the study.

3.1.4 | Other Measurements

TT intervention was associated with a reduction of type-2 inflammation, as shown in the Alluvial plot in Figure 5. Geometric mean (SD) FeNO reduced from 3.3 (0.9) to 3.0 (0.7) over the course of the study, ratio of geometric means 0.75 (95% CI: 0.45 to 0.91, $p=0.006$). Mean blood eosinophils reduced from 0.30 (0.16) to 0.15 (0.11), difference −0.16 (95% CI: −0.20 to −0.11, $p<0.0001$).

The change in ACQ, AQLQ, or SGRQ was not associated with baseline FEV_1/FVC, log FeNO, blood eosinophils, or composite T2 biomarker status; $p>0.05$ for all analyses.

One participant was admitted to hospital due to an infective exacerbation of asthma. There were no other serious adverse events and no deaths.

4 | Discussion

This feasibility study has confirmed that a randomised controlled trial of protocolised treatable trait management is acceptable to participants with asthma who are not under the care of a severe asthma clinic. Furthermore, treatable trait-guided asthma management was associated with significant clinical benefit in terms of lung function, asthma control, and quality of life. However, this improvement was at the cost of marked systemic corticosteroid exposure resulting from the escalation of treatment intensity in an attempt to reduce markers of airways inflammation, and multiple traits remained untreated at the end of the intervention.

The purpose of this study was to assess the feasibility of a future RCT comparing treatable trait-based asthma management with usual care. An important limitation is that recruitment ceased after 4 of the intended 25 participants were recruited in Australia because of difficulties associated with the COVID-19 epidemic, and this may affect the estimation of likely recruitment rates. The New Zealand site was less affected by COVID-19 disruption, and the observed recruitment rates suggest that recruitment is feasible but requires a large number of potential participants to be contacted. While 69% of screened participants were successfully enrolled, the enrolled participants represent only 8% of those initially contacted. Many of these initial contacts were via social media, and this experience of a large potential population but relatively low conversion rate is consistent with previously reported data on recruiting through social media [13]. For those who were willing to enrol, acceptability was high. Protocolised management was acceptable to the majority of participants (92%) and the majority (92%) of participants would be willing to be enrolled in a future RCT.

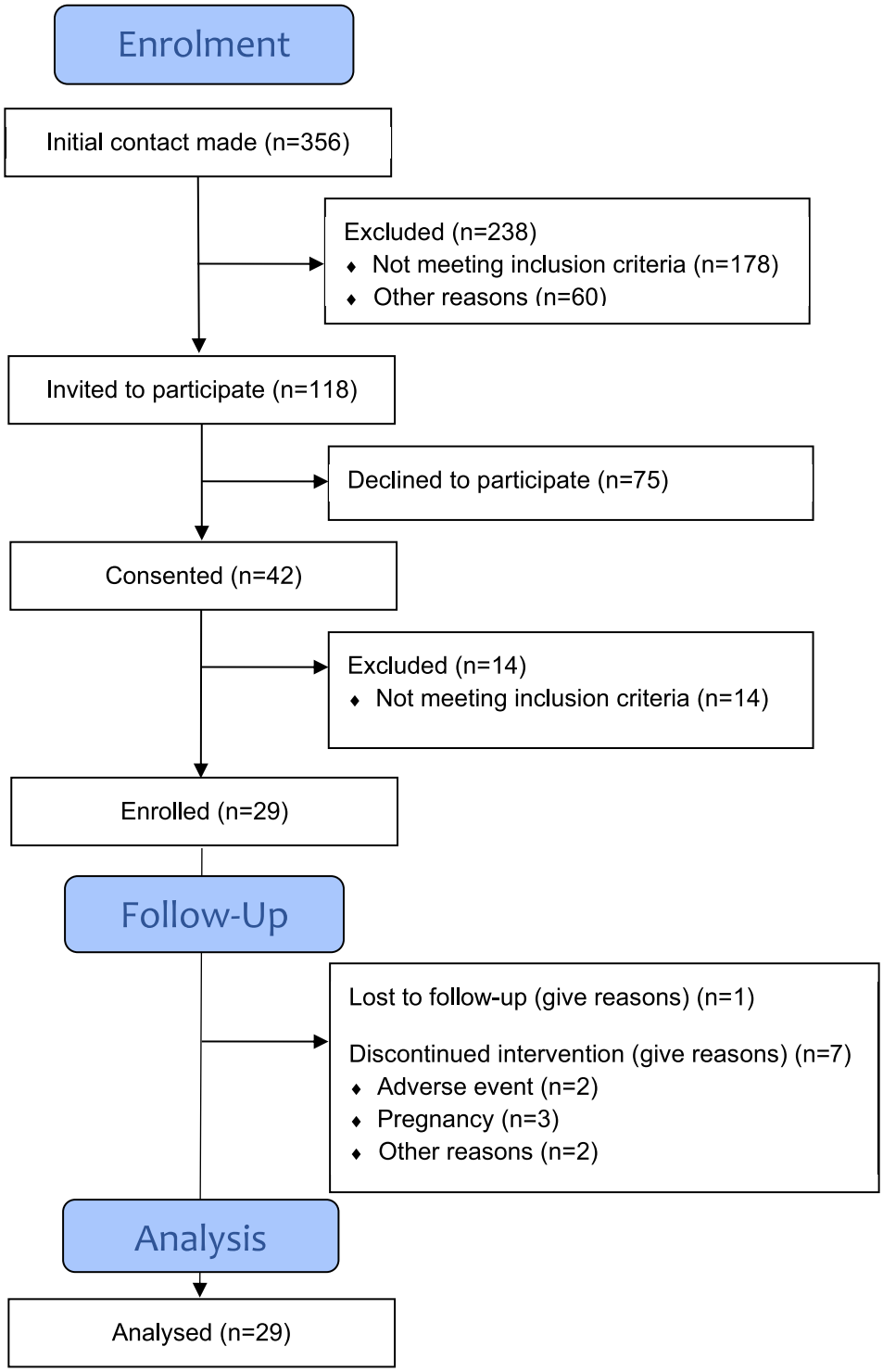

FIGURE 2 | Participant flow through the study.

The algorithmic adjustment of inhaled corticosteroids and bronchodilators used in this study is different from those utilised in previous inflammatory studies which used FeNO, blood eosinophils, or induced sputum measurements to guide the escalation of treatment [14, 15]. This is because a program of studies has clearly shown that as-needed budesonide-formoterol is superior to PRN salbutamol or terbutaline for asthma control and exacerbation risk [16–19]. Accordingly, the Global Initiative for Asthma (GINA) has listed as-needed ICS-formoterol as the preferred treatment approach for all patients with asthma, either as as-needed therapy in mild asthma or as maintenance and reliever therapy in moderate to severe asthma. With anti-inflammatory reliever therapy now recommended for all patients with asthma, the current study management algorithm is built on an anti-inflammatory reliever backbone rather than separate ICS and bronchodilator used previously.

Participation in the study was associated with clinically relevant improvements in asthma control, quality of life, markers

TABLE 3 | Baseline data for participants.

All			
Variable	**Mean (SD)**	**Median (IQR)**	**Min to max**
Age (years) $N=29$	44 (14.4)	45.7 (31.7 to 54.1)	21.3 to 66
Age at diagnosis (years) $N=29$	18.1 (15.4)	15 (5 to 30)	0 to 48
Pack years $N=13$	8.3 (8.4)	5 (2 to 10)	0 to 25
Number of severe exacerbations of asthma in the last 12 months $N=28$	2.2 (1.5)	2 (1 to 3)	1 to 7
ACQ $N=29$	2.6 (0.7)	2.4 (2.2 to 2.8)	1.6 to 4
On treatment FEV_1 (L) $N=29$	2.9 (0.9)	2.9 (2.3 to 3.5)	1.3 to 4.4
FEV_1% predicted $N=29$	89.1 (26.9)	88 (75.6 to 102.3)	49.6 to 184.2
FEV_1% change from baseline with salbutamol $N=27$	15.7 (18.8)	9.6 (5.2 to 19.3)	−4.2 to 84.2
FeNO (ppb) $N=29$	41 (37.8)	24.3 (17.7 to 49.7)	5 to 139.7
Variable	**All, *N*/29 (%)**	**Wellington, $N=25$ (%)**	**Newcastle, $N=4$ (%)**
Sex, Female	20 (69.0)	16 (64.0)	4 (100.0)
Baseline treatment			
SABA	21 (72.4)	18 (39.1)	3 (75.0)
ICS	4 (13.8)	4 (8.7)	0 (0)
LAMA	1 (3.4)	1 (2.2)	0 (0)
LTRA	1 (3.4)	1 (2.2)	0 (0)
ICS/LABA	25 (86.2)	22 (47.8)	4 (100.0)
Baseline corticosteroid level			
Level 1 (≤ FP 250 mcg/day)	8 (27.6)	6 (24.0)	2 (50.0)
Level 2 (250 mcg < FP ≤ 500 mcg/day)	15 (51.7)	14 (56.0)	1 (25.0)
Level 3 (500 mcg< FP ≤ 1000 mcg/day)	6 (20.7)	5 (20.0)	1 (25.0)
Baseline inhaler technique satisfactory	17 (68.0) $N=25$	16 (76.2) $N=21$	1 (25.0)
Admitted to hospital for asthma ever	10 (34.5)	8 (32.0)	2 (50.0)
Smoking history			
Never	16 (55.2)	13 (52.0)	3 (75.0)
Current	5 (17.2)	5 (20.0)	0 (0)
Former	8 (27.6)	7 (28.0)	1 (25.0)

Abbreviations: ACQ, Asthma Control Questionnaire; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in one second; FP, fluticasone proprionate; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, short acting beta-agonist.

of type-2 inflammation, and FEV_1. The findings are consistent with significant benefit from treatable trait guided asthma management, but this requires confirmation in a future randomised controlled trial with a comparator arm of usual care. The relative contribution of anti-inflammatory treatment, bronchodilators, and other factors associated with involvement in a clinical trial, such as increased adherence, cannot be determined from this dataset. Twenty-eight percent of participants were on low-dose maintenance ICS or as-needed ICS-formoterol at baseline despite not well-controlled asthma and previous exacerbation, so they were not on guideline-recommended treatment at the start of the study. This reflects the real-world primary care population recruited.

Despite improvements, a large proportion of patients remained symptomatic and continued to have a high trait burden from extra pulmonary and behavioural and risk factor traits. The trait identifying markers (TIMs) used in this study identify possible

TABLE 4 | Estimated trait prevalence at final visit.

Trait	*N*/26 (%)
Smoker	5/23 (22)
Airway pathogen colonisation	1/4 (25)
Frequent chest infection	8 (31)
Rhinitis/sinusitis	11 (42)
Dysfunctional breathing	8 (31)
Vocal cord dysfunction/ILO	15 (58)
Depression	3 (12)
Anxiety	12 (46)
Sub-optimal adherence	14/25 (56)
Adherence not accurate (≥1 inhaler not returned)	15/29 (52)[a]
Systemic inflammation	5 (17)
Occupational exposure	
Work ever made chest tight or wheezy	10/25 (40)
Ever had to change or leave job because it affected breathing	4 (15)
Ever worked a job which exposed you to vapours, gas, dust, fumes	14 (54)
At least one of the above	18 (69)

[a]*N* = 29 as based on inhaler returns during the study so not confined to the 26 who attended for a final visit.

traits, not confirmed diagnoses, so trait prevalence is only estimated. However, the rates described are consistent with registry data for patients with severe asthma [20]. These data suggest that for patients with uncontrolled asthma and a history of exacerbation, a more comprehensive treatable traits approach may be required to address additional outcomes of importance to patients with asthma. Versions of these two approaches have been tested in two RCTs of treatable trait-guided management in severe asthma. The Refractory Asthma Stratification Programme (RASP) study of inflammatory guided asthma management did not demonstrate a reduction in corticosteroid use in the intention to treat population, although corticosteroid down-titration was successful and associated with clinical benefit in the per-protocol population. In the other RCT of multidimensional assessment, which targeted multiple traits, this approach led to improved asthma control and quality of life with reduced healthcare utilisation [21, 22]. It is likely that differences in outcome relate, at least in part, to multi-dimensional assessment addressing a wider range of traits. However, given the large number of patients who did not follow treatment advice in the RASP study, increased adherence related to having an individual case manager may also have been a factor. This demonstrates the established importance of targeting the trait of adherence in clinical trials and practice.

Treatable trait-based approaches represent complex interventions. The two-trait optimisation approach used in this study gave rise to 11 possible treatment combinations, and this will increase exponentially with each additional trait targeted. This complexity of treatment combinations is an inherent part of treatable trait-based management and is a strength, as it allows for personalised medicine, reflecting the needs of the individual. The intervention being tested is therefore the overall treatment model of care, rather than the individual components [23]. Given this complexity, we screened for a manageable sub-set of the large number of candidate treatable traits that have been described, based on our judgement of traits which appeared identifiable, prevalent, associated with clinically important outcomes and treatable [4]. Currently, treatable trait-based asthma care is rarely available outside the setting of a severe asthma clinic. A systematic review and meta-analysis that evaluated studies that targeted at least one treatable trait from each domain of pulmonary, extrapulmonary, and behavioural/risk factors highlighted that only one of the 11 included studies was conducted in a primary care setting [24]. The results of this study are generalisable to people managed in primary care with not well-controlled asthma and an exacerbation in the previous year, although limited resourcing and access to investigations and treatments inherently restrict implementation of the treatable traits approach in this setting [25]. Nurse-led primary care services for other areas of chronic disease have proven efficacious [26] and may be an efficient model for the provision of trait-based asthma care if appropriately supported, as algorithmically adjusted management is highly implementable in primary care. Given the existing evidence base for individual traits, an alternative to a conventional randomised trial would be a cluster randomised or stepped wedge implementation study. This could determine the effectiveness of implementing a treatable trait-based community asthma referral service. However, this may not be as well-placed to determine the relative contribution of focused versus extended trait evaluation.

An important consideration for an RCT or implementation study of this approach is the degree of corticosteroid exposure associated with attempting to suppress type 2 inflammation. The clinical improvement and reduction in type 2 biomarkers demonstrated in this study were in association with relatively intensive treatment. The majority of participants were receiving high-dose inhaled corticosteroids by the final visit, and 41% were started on continuous oral corticosteroids at some point during the study. The maximum oral corticosteroid dose used in this study, prednisone 20 mg daily, is the same as that used in the RASP study of biomarker-directed treatment in severe asthma [22]. As the design of this study was a short-term feasibility study, we did not include a treatment de-escalation plan; however, a long-term study would require this option to minimise systemic corticosteroid exposure. In this study, there were patients who required oral corticosteroids who may benefit from biologics targeting type 2 inflammation; however, there are others who achieve a symptom benefit from oral corticosteroids who were not prone to frequent exacerbations and therefore would not meet current requirements to access biologics. This issue of significant corticosteroid burden can also arise when targeting asthma control with conventional symptom-based stepwise treatment escalation, as

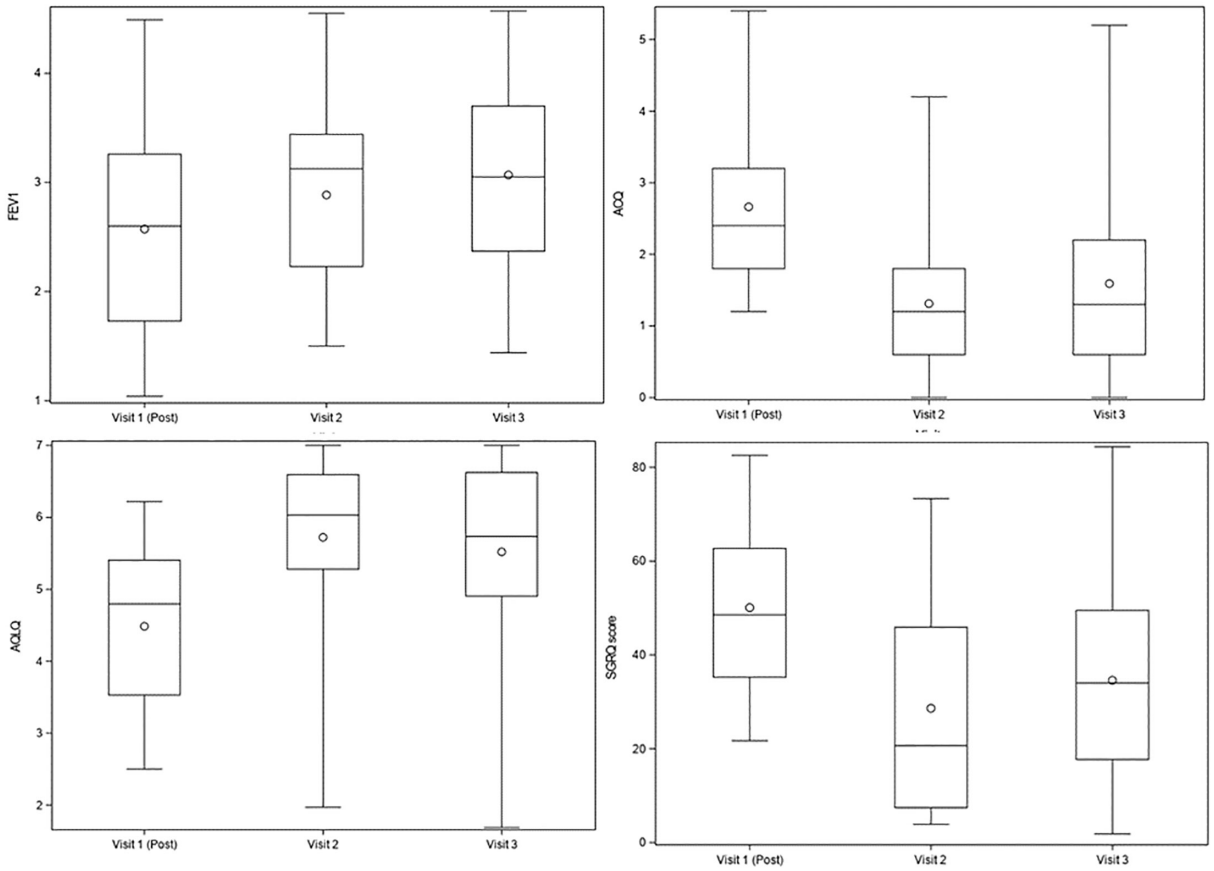

FIGURE 3 | FEV_1 and PROM change during the study. The four sub-panels show changes in FEV_1 in litres as well as ACQ, AQLQ, and SGRQ scores during the course of the study.

TABLE 5 | Treatment allocation during the study.

	Baseline, *N*/29 (%)	Treatment period 1, *N*/29 (%)	Treatment period 2, *N*/22 (%)
Corticosteroid treatment level			
1 (≤ FP 250 mcg/day)	8 (28)	0 (0)	0 (0)
2 (250 mcg< FP ≤500 mcg/day)	15 (52)	10 (34)	2 (9)
3 (500 mcg< FP ≤1000 mcg/day)	6 (21)	13 (45)	9 (41)
4 (500 mcg < FP ≤1000 mcg/day plus 10 mg/day oral prednisone)	0 (0)	6 (21)	8 (36)
5 (500 mcg < FP ≤1000 mcg/day plus 20 mg/day oral prednisone)	0 (0)	0 (0)	3 (14)
Long-acting muscarinic antagonist (yes)	0 (0)	12 (41)	12 (55)

demonstrated in the GOAL study [27]. The treatment thresholds for this study were relatively aggressive, in part to try to avoid the issues seen in other studies of biomarker-directed therapy where there was limited separation of treatment received between standard care and biomarker-directed groups. However, the OCS burden is considered unacceptable, and a future implementation of this approach would require algorithm redesign to align with the principles of oral corticosteroid stewardship [28]. Practically, this would require alternative type 2 add-on therapy such as type 2 biologics and/or azithromycin, or accepting undertreatment of the type 2 inflammation trait [29, 30].

For those patients who do not have other traits likely to be amenable to intervention, this raises the question of what level of control is desirable for the clinician and patient. Patients often judge their level of asthma control to be acceptable when clinicians would consider them to be poorly controlled [31].

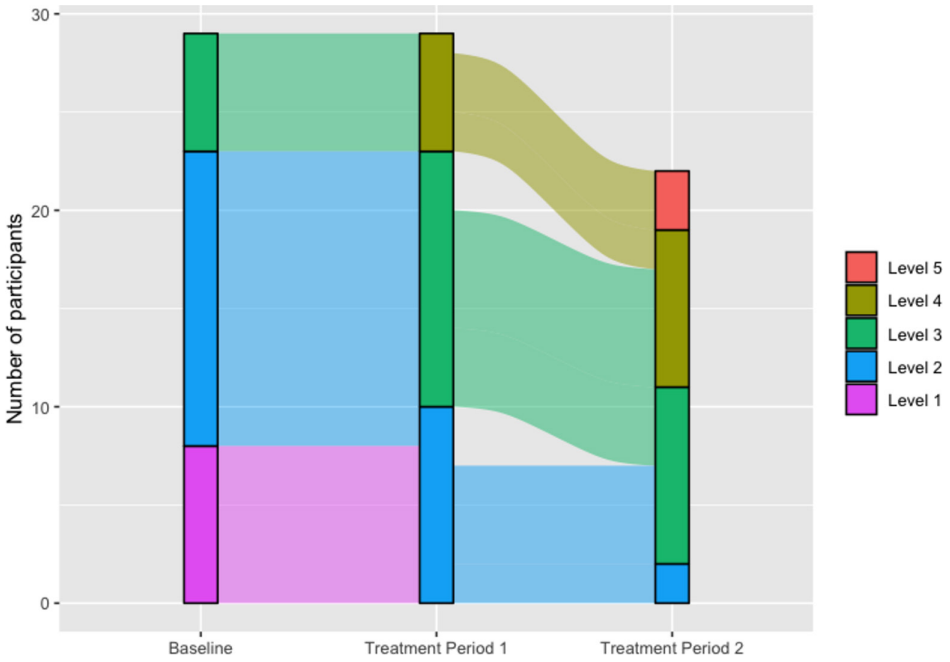

FIGURE 4 | Corticosteroid treatment level. Figure shows corticosteroid treatment level during the study. Details of corticosteroid treatment levels are given in Table 1d.

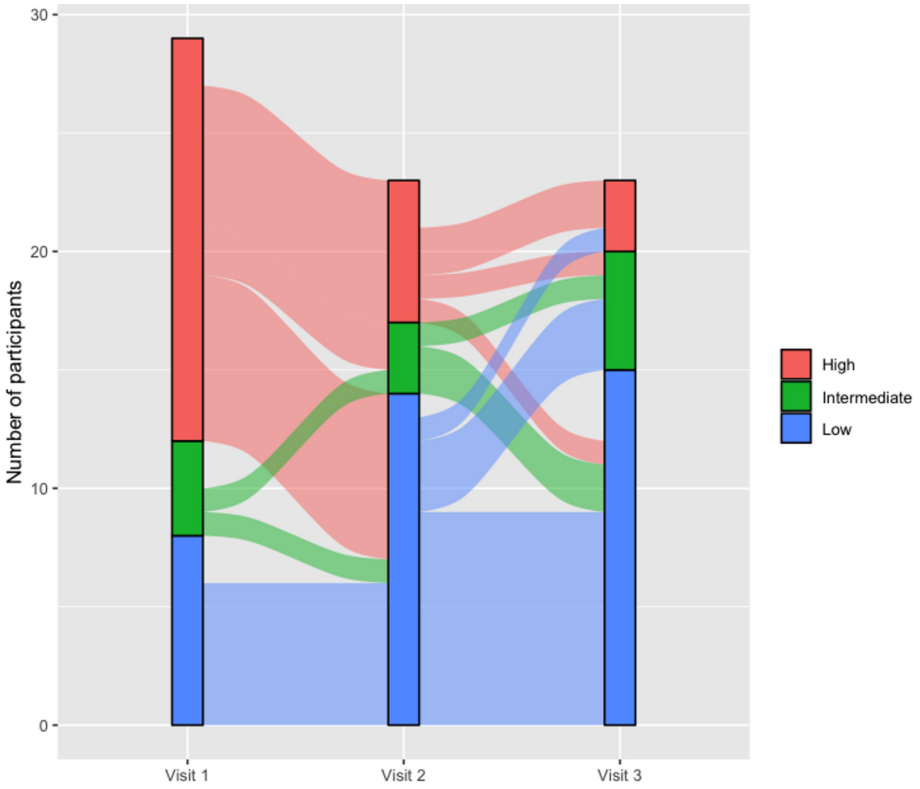

FIGURE 5 | Composite biomarker status.

With the current evidence base and accepted indications for biologics, there is a corridor of uncertainty for those patients who cannot achieve good control without very high ICS doses or even maintenance OCS and yet may not meet local funding criteria for biologics. These cases require careful consideration of the risks and benefits of corticosteroid exposure and shared decision making.

In conclusion, protocolised treatable trait-based asthma management was acceptable to patients not under the care of a severe asthma clinic, associated with significant clinical benefit, and a full trial appears feasible. Targeting airflow obstruction and type 2 inflammation was insufficient to control asthma in the majority of patients over the timeframe of this study, despite high systemic corticosteroid exposure.

Author Contributions

James Fingleton: conceptualization (lead), data curation (equal), formal analysis (supporting), funding acquisition (lead), investigation (equal), methodology (lead), project administration (equal), supervision (equal), writing – original draft (lead), writing – review and editing (equal). **Rob McLachlan:** data curation (equal), investigation (equal), writing – review and editing (equal). **Jenny Sparks:** data curation (equal), investigation (equal), methodology (supporting), project administration (equal), writing – review and editing (equal). **Richard Beasley:** conceptualization (supporting), formal analysis (supporting), funding acquisition (supporting), methodology (supporting), writing – review and editing (equal). **Alvar Agustí:** conceptualization (supporting), formal analysis (supporting), funding acquisition (supporting), methodology (supporting), writing – review and editing (equal). **Peter G. Gibson:** conceptualization (supporting), formal analysis (supporting), funding acquisition (supporting), methodology (supporting), writing – review and editing (equal). **Ian D. Pavord:** conceptualization (supporting), formal analysis (supporting), funding acquisition (supporting), methodology (supporting), writing – review and editing (equal). **Jo Hardy:** conceptualization (supporting), methodology (supporting), writing – review and editing (equal). **Mark Weatherall:** conceptualization (supporting), formal analysis (supporting), funding acquisition (supporting), methodology (supporting), writing – review and editing (equal). **Allie Eathorne:** formal analysis (lead), methodology (supporting), visualization (lead), writing – review and editing (equal). **Vanessa M. McDonald:** conceptualization (supporting), data curation (supporting), formal analysis (supporting), funding acquisition (supporting), investigation (equal), methodology (equal), project administration (equal), supervision (equal), writing – review and editing (equal).

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Treatable Traits Study Group:

Chief Investigator and New Zealand Principal Investigator: Dr. James Fingleton.

Australia Principal Investigator: Prof. Vanessa M. McDonald.

Steering Committee:

Dr. Jo Hardy, Medical Research Institute of New Zealand, Wellington, New Zealand.

Dr. Rob McLachlan, Medical Research Institute of New Zealand, Wellington, New Zealand.

Prof. Peter G. Gibson, University of Newcastle, Newcastle, Australia.

Prof. Ian D. Pavord, University of Oxford, Oxford, United Kingdom.

Prof. Alvar Agusti, University of Barcelona, Barcelona, Spain.

Prof. Mark Weatherall, University of Otago Wellington, Wellington, New Zealand.

Prof. Richard Beasley, Medical Research Institute of New Zealand, Wellington, New Zealand.

Site Investigators:

Wellington, NZ.

Augustus Anderson, Luisa Diputado, Allie Eathorne, Dr. James Fingleton, James Gilchrist, Dr. Jo Hardy, Mark Holliday, Kyley Kerse, John Martindale, Dr. Rob McLachlan, Nick Shortt, Jenny Sparks.

Newcastle, Australia.

Prof. Vanessa McDonald, Prof. Peter Gibson, Jasminka Nikolajevic-Sarunac, Amber Smith, Paola Urroz. James Fingleton, Vanessa M. McDonald, Jo Hardy, Rob McLachlan, Peter G. Gibson, Ian D. Pavord, Alvar Agusti, Mark Weatherall, Richard Beasley, Augustus Anderson, Luisa Diputado, Allie Eathorne, James Fingleton, James Gilchrist, Jo Hardy, Mark Holliday, Kyley Kerse, John Martindale, Rob McLachlan, Nick Shortt, Jenny Sparks, Vanessa McDonald, Peter Gibson, Jasminka Nikolajevic-Sarunac, Amber Smith, Paola Urroz. Open access publishing facilitated by University of Otago, as part of the Wiley - University of Otago agreement via the Council of Australian University Librarians.

Ethics Statement

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by the Central Health and Disability Ethics Committee—approval: 20/CEN/33. All adult participants provided written informed consent to participate in this study.

Conflicts of Interest

J.F. reports personal fees and non-financial support from AstraZeneca and GSK outside the submitted work. R.B. reports research funding from AstraZeneca, Genentech, Teva, and Cure Kids NZ, and personal fees from AstraZeneca, Teva, Avillion, and Cipla; outside the submitted work. A.A. reports research funding from AstraZeneca, GSK, and the Menarini Foundation, and personal fees from AstraZeneca, Chiesi, GSK, the Menarini Foundation, MSD, Sanofi, and Zambon; outside the submitted work. P.G.G. reports research funding from GSK and personal fees from AstraZeneca, GSK, Novartis, and Sanofi; outside the submitted work. I.D.P. reports research funding, personal fees, and non-financial support from Aerocrine, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Roche-Genentech, GSK, Knopp, Merck, Novartis, Sanofi-Regeneron, and Teva; outside the submitted work; and royalties related to the Leicester Cough Questionnaire from Bayer, Ismed, and Merck outside the submitted work. J.H. reports non-financial support from AstraZeneca outside the submitted work. V.M.M. reports personal fees and non-financial support from GSK, Boehringer Ingelheim, and the Menarini Foundation outside the submitted work. A.E., J.S., M.W., and R.M. declare no conflicts of interest. R.B. and V.M.M. are Editorial Board members of Respirology and co-authors of this article. They were excluded from all editorial decision-making related to the acceptance of this article for publication.

Data Availability Statement

Data available on request from the authors.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.