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Early View

Original research article

Factors affecting adherence with treatment advice in a clinical trial of patients with severe asthma

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Factors affecting adherence with treatment advice in a clinical trial of patients with severe asthma.

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Take Home Message

Belonging to a minority ethnic group, multiple prior changes in medication, being treated at a specific clinical centre, introduction of systemic corticosteroids and increased asthma symptoms were associated with resistance to treatment modification.

ABSTRACT

BACKGROUND: Understanding why patients with severe asthma do not follow healthcare provider (HCP) advice to adjust treatment is critical to achieving personalised disease management.

METHODS: We reviewed patient choice to follow HCP advice to adjust asthma treatment in a randomised, controlled, single-blind (study participant), multi-centre, parallel group 48-week clinical study comparing biomarker directed treatment adjustment to standard care in severe asthma.

RESULTS: Of 1572 treatment advisories (301 participants), instructions were followed in 1,377 cases (87.6%). Patients were more likely to follow advice to remain on treatment (96.7%) than to either reduce (70.3%) or increase (67.1%) their treatment, with 64% of patients following all treatment advice. Multivariate analysis associated belonging to an ethnic minority group (OR: 3.10; 95% CI: 1.68, 5.73) and prior study medication changes (≥2 OR: 2.77, 95% CI: 1.51, 5.10) with failure to follow treatment advice. In contrast, emergency room attendance in the prior year (OR: 0.54, 95% CI: 0.32, 0.92) was associated with following treatment advice. The largest effect was seen with transition onto or off oral corticosteroids (OR: 29.28; 95% CI: 16.07, 53.36) when compared to those requested to maintain treatment. Centre was also an important determinant regarding the likelihood of patients to follow treatment advice.

CONCLUSIONS: Belonging to an ethnic minority group and multiple prior treatment adjustments were associated with not following HCP treatment advice. Patients also responded differently to HCP advice across UK specialist centres. These findings have implications for generalisability for models of care in severe asthma and require further focussed studies.

Key words: severe asthma; ethnic minority group; treatment advice

INTRODUCTION

Asthma treatment guidelines advocate that treatment is increased to reduce symptoms and risk of asthma exacerbations, with consideration of treatment reduction when asthma is controlled for a period of at least 3 months [1]. This strategy requires partnership between patients and healthcare professionals (HCP) to adjust treatment when appropriate, particularly among those patients on high dose corticosteroid treatment [2–4].

In a recent study, we investigated two strategies for adjusting corticosteroid therapy (both inhaled and oral) in patients with severe asthma: type-2 inflammation (T2)-biomarker adjustment versus adjustment using current symptoms and recent asthma exacerbation history [5]. The study was designed primarily to explore the impact of corticosteroid treatment reduction in T2-biomarker low participants. Clear clinical benefits were seen using biomarker-based treatment adjustment in patients who followed the study treatment algorithms (pre-specified per protocol analysis), which included a greater proportion of patients on lower dose of inhaled corticosteroids (ICS) and reduced risk of exacerbation [5]. Despite these benefits, a large proportion of patients did not follow HCP recommendations to modify treatment. A reluctance to change therapy was anticipated for treatment increase, often meaning starting oral corticosteroids (OCS) but not to reduce therapy in a study where patients were advised the primary aim was to reduce corticosteroid treatment.

Asthma guidelines distil an extensive scientific literature into evidence-based treatment pathways. However, effective implementation depends on patient engagement. We explored demographic and clinical factors to identify patient barriers to following HCP advice to adjust treatment.

METHODS

Patients and study design

We performed a post-hoc secondary analysis of data from our randomised, controlled, single-blind (study participant), multi-centre, parallel group 48-week clinical study in patients with severe asthma (Global Initiative for Asthma steps 4 and 5 classification of asthma severity) (ClinicalTrials.gov: NCT02717689) [5,6]. The study team included a Patient Input Platform (PIP), a panel of patients with an insight into clinical trials who provided direction regarding patient needs and how to facilitate their understanding of study aims, objectives, and requirements. This group, recruited by Asthma-UK, was embedded in all discussions relating to study design and implementation. The protocol was reviewed and approved by the Office for Research Ethics Northern Ireland (NI0158) and obtained local National Health Service Research and Development approval for individual sites. All patients provided written informed consent for study participation.

Study procedures

Following randomisation, patients attended the clinic every 8 weeks for review of asthma control and treatment and the electronic case report form software processed the study algorithms to generate a treatment advisory in both treatment arms to decrease, maintain or increase treatment. In brief, we compared a composite biomarker-based adjustment of corticosteroid therapy (using a composite index of blood eosinophil count, serum periostin, and FeNO concentration) with adjustments using a control-arm algorithm based on asthma symptoms, lung function, and recent exacerbation history. The term 'advisory' was specifically chosen as it was anticipated that some patients would not follow treatment advice e.g., progression to OCS. In keeping with the pragmatic nature of the study, patients were permitted to stay in the study if treatment advice was not followed although the reasons for this were recorded at the subsequent study visit. Treatment advisories not described in the study protocol (patient on lowest allowed ICS dose, low cortisol preventing prednisolone reduction) or where other external factors influenced the patient's choice to adjust treatment (clinician decision to override treatment adjustment or site logistical error) were interpreted as patient following HCP advice (described in **Supplementary Table E1a and Table**

E1b). When a treatment advisory could not be generated (primarily due to a missing biomarker measurement) a default 'maintain treatment' advisory was generated.

Statistical analyses

Descriptive statistics are presented as means (SD), medians [IQR] or counts (%) as appropriate. Comparisons between patients who followed all treatment advice during the study and those who did not follow at least one advisory were made using t-tests (normally-distributed variables), Mann-Whitney U tests (non-normally distributed variables) or Chi-square tests (categorical variables). Initial univariate logistic regression models were used to assess the association for a broad range of demographic and clinical variables that could plausibly impact the patient's decision to follow treatment advisories. A final multivariate model was selected using a modified form of backward selection. Our initial models investigated all advisories combined, however we fitted separate models estimating the probability of following a reduce, maintain or increase advisory. To investigate potential outcome misclassification (due to intentional or unintentional patient misreporting) we compared reported medication adjustment with change in T2-biomarkers, known to be highly corticosteroid sensitive [9].

Supplementary analysis compared exacerbation risk among those with a disassociated symptom/biomarker profile. A subgroup of patients with low symptoms and moderate/high biomarkers was identified, as was a separate subgroup with high symptoms and moderate/low biomarkers (see **Supplementary Appendix**). The outcome measure was the time to the first exacerbation within the 8-week study period with patients considered 'at risk' from the date of the study visit until the day prior to next study visit (follow-up truncated at 56 days). Comparisons were investigated using Kaplan-Meir plots, and Cox regression models adjusted for age, gender and treatment centre were used to conduct hypothesis tests. Full details of the statistical methods are provided in **Supplementary Appendix**. Analyses were conducted using STATA 16 (StataCorp, Texas, USA).

RESULTS

Patients (n=301) undertook 1,629 visits during the course of the study; of these, 25 visits had missing data. There was no information on whether or not the treatment advice was followed for 26 visits (26 patients). In six further cases it was unclear why treatment advice was not followed. Of the remaining 1572 treatment advisories issued, 1,377 (87.6%) were followed. Patients were more likely to follow advice to remain on current treatment (96.7%) than advice to either reduce (70.3%) or increase treatment (67.1%) (**Supplementary Table 1a and 1b**). Where treatment advisories were reported as either followed or not followed, change in individual T2 biomarkers was consistent with accurate self-reporting of treatment (**Supplementary Table 1c**).

Baseline demographic and clinical factors in patients who followed all treatment advice (n=186, 64%) and those who decided not to follow at least one treatment advisory (n=105, 36%) are summarised in **Table 1**. Minority ethnic group (13.3% vs. 4.3%; p=0.005) and higher intensity ICS dose (2418 [873] vs. 2151 [608] μg BDP equivalent; p=0.002) were associated with not following treatment advice, whereas patients on maintenance OCS at study entry (41.4%vs. 28.6%; p=0.029) and having an emergency room attendance in the 12 months before randomisation (25.8% vs. 15.2%; p=0.037) were less likely to not follow advice. There was wide variation in the way treatment advisories were followed by patients at different clinical centres (**Supplementary Table 2** and **Supplementary Figure 1**) which may be partly related to cross-site differences in the characteristics of patients enrolled (e.g., ethnicity, corticosteroid treatment intensity), though differences were also seen between sites in gender, primary care asthma attendance and asthma control (**Supplementary Table 2**).

Univariate associations with all candidate variables are displayed in the appendix (**Supplementary Table 3**). In multivariate analysis, belonging to an ethnicity minority group (OR: 3.10; 95% CI: 1.68, 5.73) and prior medication changes during the course of the study (≥2 OR: 2.77, 95% CI: 1.51, 5.10) were associated with failure to follow treatment advice, whereas an emergency room attendance in the prior year (OR: 0.54, 95% CI: 0.32, 0.92) was associated with following treatment advice (**Table 2**). The largest effect in adjusting treatment was seen with transition onto or off OCS (OR: 29.28; 95% CI: 16.07, 53.36), although patients

advised to amend OCS or ICS dose (OR: 11.75, 95% CI: 6.97, 19.78) or add/remove a long acting muscarinic antagonist (OR: 9.84, 95% CI: 4.20, 23.02) were also less likely to follow treatment advice than those asked to maintain treatment. Thus, after adjusting for other factors in the model, predictions suggest that 42.8% (95% CI: 32.6, 53.1) of patients decided not to initiate/discontinue OCS, versus only 3.6% (95% CI: 2.2, 4.9) who decided not to maintain treatment (difference: 39.3%; 95% CI: 28.9, 49.6). Study centre was an important determinant regarding the likelihood of patients to follow treatment advice, in particular patients from Site B (OR: 7.54, 95% CI: 3.46, 16.41) were much less likely to follow treatment advisories than those from other centres. For example, model predictions suggest that 28.0% (95% CI: 23.1, 32.9) of advisories were not followed at Site B versus just 3.9% (95%: 0.5, 0.7) at Site C (difference: 24.1%, 95% CI: 17.9, 30.3) after adjusting for other factors in the model.

We explored factors associated with not following advice (**Figure 1**, **Supplementary Table 4**). Minority ethnic group and multiple prior treatment changes consistently reduced the probability of a patient following treatment adjustment across all advisories. Patients with poorer asthma control (OR: 3.40; 95% CI: 1.62, 7.16) and ex-smokers (OR: 2.23, 95% CI: 1.01, 4.91) were more likely to not follow reduce advisories, although there was little effect of these factors on following maintain or increase advisories. Patients were more likely to refuse initiation of OCS (OR: 3.93, 95% CI: 1.52, 10.17), which was an anticipated pre-defined secondary outcome, when compared to advice to increase corticosteroid dose. Conversely, there was evidence of patients being more likely to follow treatment advice when asked to discontinue OCS (OR: 0.39; 95%:0.13, 1.19; p=0.097). Centre effects were broadly consistent across advisories to reduce, maintain or increase treatment, with patients treated at Site B least likely to follow advisories.

The diagnostic accuracy of the multivariate model for following treatment advice demonstrated an AUC of 0.870 (95%: 0.842, 0.899, **Supplementary Figure 2**) and was consistent for advice to both reduce (AUC: 0.826, 95%: 0.79, 0.883) and increase (AUC: 0.830, 95%: 0.780, 0.880) treatment (**Supplementary Figure 2**). The internally cross-validated AUC was similar for all analyses (e.g., all treatment advisories combined AUC: 0.858, 95% CI: 0.814, 0.882), suggesting low test error.

As current asthma symptoms impacted decisions to reduce corticosteroid treatment adversely, we analysed the impact of this decision by exploring exacerbation risk in patients where T2-biomarkers were dissociated from asthma symptoms. The symptom-based and biomarker-based algorithms are shown in **Supplementary Table 5** and demographic details in **Supplementary Tables 5, 6 and 7**; in patients with high symptoms and low/moderate T2 biomarkers, exacerbation risk was no different (HR: 0.92; 95% CI: 0.45, 1.90) when patients were managed according to symptoms (advised to increase treatment) or biomarkers (advised to maintain or reduce treatment) despite 59% of patients increasing their corticosteroid dose in the symptom based arm versus only 4% in the biomarker based arm ($p<0.001$; **Figure 2a**). However, in patients with low symptoms and moderate/high biomarkers, there was a significantly increased risk of exacerbation (HR: 2.59, 95% CI: 1.07, 6.26; **Figure 2b**) when patients were managed according to symptoms (advised to reduce treatment) compared to those treated according to biomarker score (advised to maintain or increase treatment).

DISCUSSION

We explored reasons for patients not following HCP advice in a clinical trial comparing T2 biomarker-directed corticosteroid treatment with standard care in people with severe asthma. We reclassified any scenario where an external factor (e.g., advice from HCP to not follow the advice), interfered with the patient decision to follow the treatment, thus ensuring a focus on patient directed decisions. Detailed patient information about the study explicitly described how treatment adjustment would be based on biomarker treatment in 80% taking part in in the study (4:1 randomisation to T2-biomarker directed treatment). It is generally assumed that adherence to treatment in clinical trials is high [11], however, extensive evidence exists to the contrary [12]. The possible reluctance to initiate OCS was anticipated, thus adherence with all treatment adjustments was carefully captured at sequential study visits, allowing further analysis of the factors influencing this behaviour [5] and change in T2-biomarkers was consistent with accurate patient self-reporting of treatment.

Belonging to a minority ethnic group was consistently associated with patients not following treatment advice irrespective of type. Poorer asthma outcomes and different patterns of health-service use have previously been described in UK patients with asthma from ethnic minority backgrounds [13]. It is generally accepted that ethnic diversity is inadequately reflected in clinical trials, and potentially limits the applicability of results to the wider population [14, 15]. All patients were approached to take part in the clinical trial after assessment by investigators to ensure they understand the study aims and can comply with the study protocol. In this context, issues such as language barriers and comprehension of the goals of the study seem unlikely to explain ethnic differences in patient adherence to treatment guidance and further work is required to explain our observation.

Prior medication changes during the course of the study, were associated with patients subsequently deciding not to follow further treatment adjustment and importantly, this was consistent whether treatment was being increased or reduced. Where treatment is frequently adjusted, it seems logical to assume that patients decide further adjustments will not be beneficial, particularly if advice contradicts prior changes. It is also recognised that in severe asthma, more complex multi-modality drug regimens are

associated with treatment non-adherence [16]. Adherence with advice to maintain treatment was extremely high (97%); however, we did not predict the low level of adherence with treatment advice observed during our study and hence this is a post-hoc analysis with no pre-specified analysis plan. Consequently, our results should be interpreted as exploratory, but future studies of biomarker directed treatment in asthma should include detailed analysis of adherence with study advice and patient adherence to this advice. The apparent reluctance to adjust established treatment has potential implications for Asthma Guidelines, which currently suggest treatment reduction after periods of asthma stability, and treatment increases if asthma control deteriorates. It should be noted that while individual components of these guidelines have been formally tested, the overall benefit of a step-wise model of care included in asthma guidelines has not been formally validated in a controlled clinical trial. A more successful strategy, particularly in cases of more severe asthma that could progress to high dose ICS, may be to target treatment using predictive biomarkers of therapeutic response on first presentation and maintain patients on this 'correct' treatment when stable [17, 18].

Marked variation in patients following treatment advice was seen across different clinical centres (particularly one centre), which occurred consistently irrespective of the type of advice given. Some of the variability may be explained by centre differences in the patient population, it also suggests that patient willingness to adjust treatment was substantially different between centres. This heterogeneity is surprising considering the specialist nature of the centres, and since the intention to adjust treatment had been communicated clearly to patients as a core study aim. It may reflect a patient's belief that they were currently on 'optimal' treatment and lack of confidence that the provided advice was correct. Whatever the mechanism, it is an important observation as even under the tight constraints of a clinical trial, with standardized algorithms and training of site staff relating to treatment adjustment, patient behaviour differed markedly between clinical centres. Further work is needed to clarify why there was such disparity between centres. Prior patient experience of biomarker directed care is a potential factor, particularly when these dissociate from symptoms. There are clearly implications around implementation of any future

models of asthma care that requires treatment adjustment as this may be differentially acceptable to individual patients being managed at different clinical centres.

Recent emergency room attendance was associated with patients following treatment advice, potentially as this recent 'watershed' event may make patients more engaged in treatment advice and more open to the benefits of changing treatment. Poor adherence with asthma treatment has consistently been shown to be associated with increased emergency room visits [19] but our findings suggest that a prior emergency room visit is also associated with a greater willingness to increase treatment suggests this may be a bidirectional relationship. Not following advice to initiate OCS was anticipated reflecting patient dislike of their well-recognised side-effects [2, 20, 21]. However, lack of engagement with treatment adjustment was evident across all therapeutic changes, consistent with a general reticence to adjust any form of treatment.

The accuracy of the multivariate model examining patient adherence with treatment advice supports our understanding that most important variables affecting patient treatment decisions were captured; however, further in-depth qualitative studies exploring the roots of these associations are required to aid the design of effective interventions. Indeed, a literature review identified six key factors that contribute to intentional non-adherence amongst older adults (illness beliefs, perceived treatment risks, benefits and necessity of potential treatments, patient–practitioner relationship, poly-pharmacy/regimen complexity and inter-current physical/mental illness) and all of the factors identified in our analysis can be mapped onto these areas [22]. The study team took advice on study design from a panel of expert patients (PIP) who advised that patients would be enthusiastic about both biomarker directed treatment and achieving low doses of corticosteroid. However, patient/public advisory groups in health research are often unrepresentative of the wider patient population, skewing towards those who are white, middle-class and older-aged. The risks overlooking some of the key barriers to study design identified in our study and, specifically, the impact of ethnicity on patient decisions, must inform PIP selection criteria for future programmes. Issues highlighted in this analysis, which impacted patient treatment decisions were not identified as potential barriers at study design. The impact of ethnicity on patient decisions must inform PIP selection criteria for future programmes.

As the study focussed on reducing corticosteroid treatment, we explored patient reasons to choose not to reduce treatment and identified being an ex-smoker and having uncontrolled asthma as key factors. The latter finding suggests that some study participants would have benefited from a more thorough explanation of the dissociation between symptoms and corticosteroid dose when T2 biomarkers are low. As prominent asthma symptoms adversely impacted on advice to reduce corticosteroid treatment, we examined exacerbation risk in patients where T2-biomarkers were dissociated from asthma symptoms. Among those with high symptoms and low/moderate biomarkers, exacerbation risk was not different when patients were asked to reduce/maintain corticosteroid treatment based on T2-biomarkers, whereas in those with high/moderate T2-biomarkers and low symptoms, exacerbation risk was higher when biomarkers were ignored when determining the treatment advisory. This increased risk of exacerbation has been described previously in sputum-guided treatment adjustment where symptom low/sputum eosinophil high patients had a 10-fold reduction in exacerbation risk when treatment was increased according to sputum eosinophilia [23]. Taken together, high levels of symptoms are associated with patients deciding not to reduce treatment where this is appropriate (T2-biomarker low) and treatment adjustment based on low symptoms (and ignoring high T2-biomarkers) is associated with increased risk. However, this study demonstrates that while T2-biomarkers provide prognostic information and correct corticosteroid treatment advice, many symptomatic patients will decide not to follow appropriate advice to reduce corticosteroid treatment.

In conclusion, we identified factors associated with patients not following HCP treatment advice within a robustly-conducted randomised controlled trial, which may be important in improving patient engagement with HCP directed advice in the routine management of severe asthma. Factors such as minority ethnic group and clinical centre require further focussed studies to explore the underlying reasons for their importance. Irrespective of the outcomes, these factors have implications for generalisability for any model of care in severe asthma.

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TABLES

Table 1. Demographics, medical history, comorbidities, lung function and corticosteroid treatment in the randomised population who followed all treatment advice and those who did not follow at least one treatment advisory

	Followed Treatment Advice (N=186)	Chose not to follow Treatment Advice (N=105)	P-Value
Age (years)	55.6 (13.7)	56.1 (12.4)	0.7790
Male	58 (31.2%)	41 (39.0%)	0.1739
Ethnic Minority Groups	8 (4.3%)	14 (13.3%)	0.0051
BMI (kg/m^2)	32.1 (7.3)	31.3 (7.0)	0.3568
Smoking status			0.5193
Never smoked	141 (75.8%)	76 (72.4%)	
Ex-smoker	45 (24.2%)	29 (27.6%)	
Atopic disease	130 (70.3%)	71 (67.6%)	0.6380
Hospital admission for asthma (previous year)	34 (18.3%)	21 (20.0%)	0.7189
Emergency room attendance for asthma (previous year)	48 (25.8%)	16 (15.2%)	0.0366
General Practitioner attendance for asthma (previous year)	107 (57.5%)	50 (47.6%)	0.1034
Rescue OCS (previous year)	2.0 (1.0,4.0)	2.0 (1.0,4.0)	0.8711
ER Asthma Admission (Ever)	34 (18.3%)	28 (26.7%)	0.0933
Ventilated (Ever)	15 (44.1%)	15 (53.6%)	0.4585
Rhinitis	128 (68.8%)	73 (69.5%)	0.9003
Eczema	67 (36.0%)	31 (29.5%)	0.2600
Nasal polyps	43 (23.1%)	27 (25.7%)	0.6188
Previous nasal surgery	40 (21.5%)	27 (25.7%)	0.4128
Oesophageal reflux	115 (61.8%)	60 (57.1%)	0.4331
Aspirin sensitivity	29 (15.6%)	16 (15.2%)	0.9362
Depression / anxiety	60 (32.3%)	31 (29.5%)	0.6290
Hypertension	59 (31.7%)	33 (31.4%)	0.9590
Osteoporosis / osteopenia	47 (25.3%)	18 (17.1%)	0.1100
Osteoarthritis	54 (29.0%)	23 (21.9%)	0.1856
Hypercholesterolaemia	39 (21.0%)	14 (13.3%)	0.1051
Diabetes	21 (11.3%)	12 (11.4%)	0.9715
Cataracts	20 (10.8%)	13 (12.4%)	0.6740
Obstructive sleep apnoea	11 (5.9%)	6 (5.7%)	0.9444
Ischaemic heart disease	9 (4.8%)	3 (2.9%)	0.4143
Peptic ulcer	4 (2.2%)	3 (2.9%)	0.7056
Stroke	2 (1.1%)	4 (3.8%)	0.1150
Chronic kidney disease	2 (1.1%)	5 (4.8%)	0.0487
Glaucoma	4 (2.2%)	0 (0.0%)	0.1302
Myocardial infarction	2 (1.1%)	1 (1.0%)	0.9206
FEV_1 (%)	75.1 (20.2)	76.4 (17.7)	0.5692
FVC (%)	90.4 (17.1)	92.1 (16.7)	0.4325
FEV1/FVC	0.66 (0.12)	0.66 (0.11)	0.8747
PEF (Litres)	366.1 (120.3)	386.5 (138.4)	0.1934
Sputum eosinophils (%)*	1.5 (0.4,7.0)	1.0 (0.3,8.3)	0.9419
FeNO (ppb)	20 (13,28)	21 (13,29)	0.8503
Blood eosinophils (10^9 cells/L)	0.20 (0.11,0.32)	0.24 (0.10,0.37)	0.3364
Periostin (ng/ml)	52.0 (13.8)	54.6 (20.1)	0.2021
Maintenance OCS user	77 (41.4%)	30 (28.6%)	0.0293
OCS dose (mg)	0 (0,8)	0 (0,5)	0.0519

ICS dose (BDP µg equivalent)	2151 (608)	2418 (873)	0.0024
ACQ-7 Score	2.1 (1.1)	1.8 (1.2)	0.0875
AQLQ Total Score	4.8 (1.3)	5.0 (1.5)	0.5433

ER = emergency room; OCS = oral corticosteroid; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; PEF = peak expiratory flow; FeNO = fractional exhaled nitric oxide; ACQ = Asthma Control Questionnaire; ICS – inhaled corticosteroid

Table 2. Multivariate analysis of factors associated with not following treatment advice (all advisories combined)

Variable	Univariate		Multivariate	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Centre				
Site A	Ref	.	Ref	.
Site B	7.44 (3.43,16.14)	0.001	7.54 (3.46,16.41)	0.001
Site C	0.46 (0.15,1.44)	0.184	0.37 (0.12,1.18)	0.094
Site D	1.31 (0.46,3.74)	0.609	1.80 (0.62,5.29)	0.282
Site E	1.94 (0.84,4.49)	0.119	1.57 (0.64,3.86)	0.322
Site F	1.57 (0.62,3.97)	0.341	1.01 (0.38,2.69)	0.987
Other	2.15 (0.98,4.69)	0.056	1.39 (0.62,3.10)	0.428
Ethnic Minority Groups	2.06 (0.95,4.46)	0.068	3.10 (1.68,5.73)	0.001
Ex-smoker	1.11 (0.69,1.80)	0.664	1.31 (0.81,2.11)	0.265
ER Visit (Last Year)	0.58 (0.32,1.04)	0.070	0.54 (0.32,0.92)	0.024
ACQ7>1.5	0.94 (0.63,1.39)	0.757	1.16 (0.79,1.70)	0.459
Previous Changes				
0	Ref		Ref	
1	1.67 (1.08,2.59)	0.021	1.89 (1.18,3.02)	0.008
2+	2.07 (1.19,3.62)	0.010	2.77 (1.51,5.10)	0.001
Treatment Adjustment				
Maintain Treatment	Ref		Ref	
Amend ICS/OCS Dose	11.58 (7.05,19.02)	0.001	11.75 (6.97,19.78)	0.001
Add/Remove LAMA	9.95 (4.82,20.53)	0.001	9.84 (4.20,23.02)	0.001
Add/Remove OCS	24.36 (13.62,43.58)	0.001	29.28 (16.07,53.36)	0.001

ER = Emergency Room; ACQ = Asthma Control Questionnaire; OCS = oral corticosteroid; ICS = inhaled corticosteroid; LAMA = long-acting muscarinic antagonist

Figure 1: Comparison of multivariate analysis for reduce, maintain and increase advisories

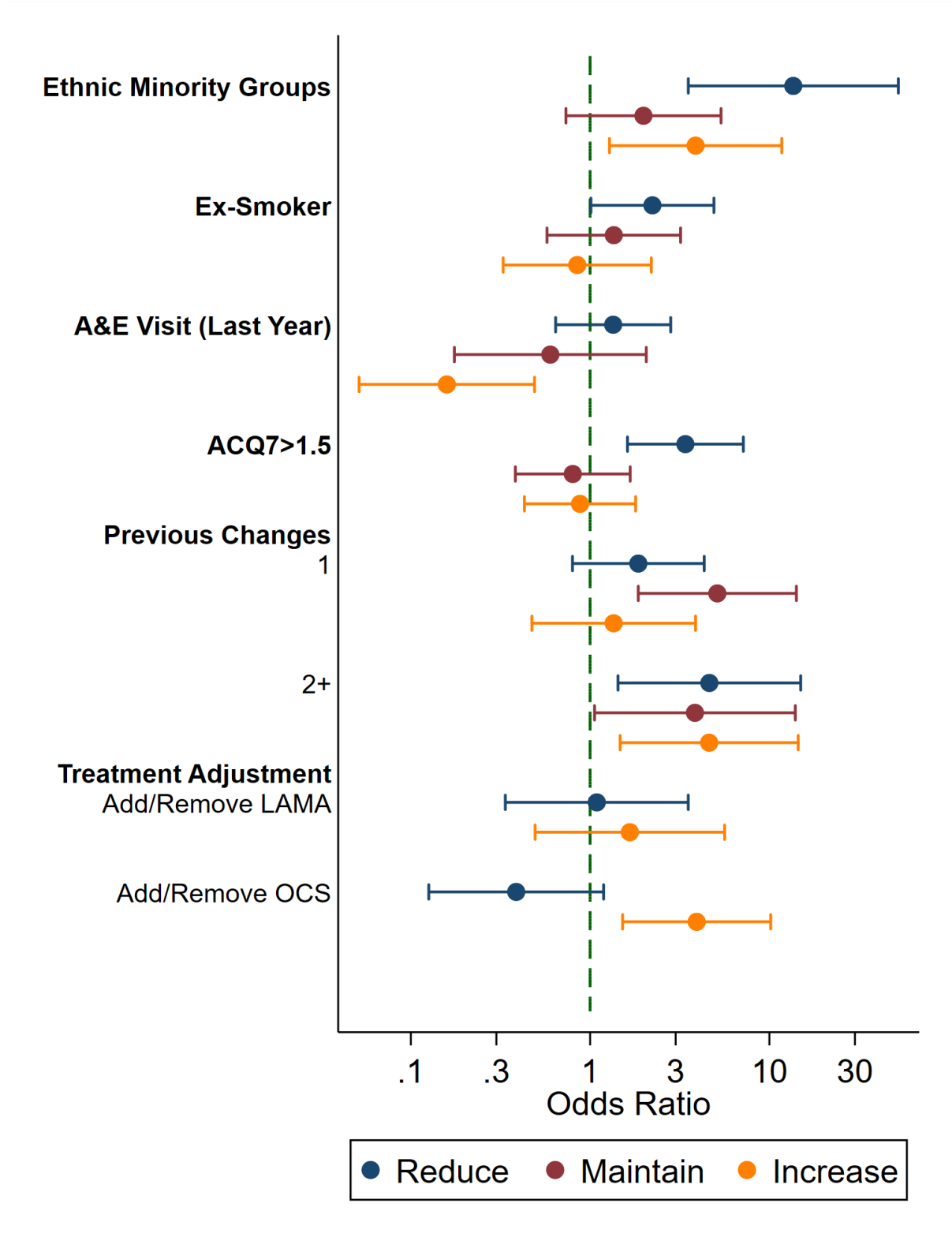
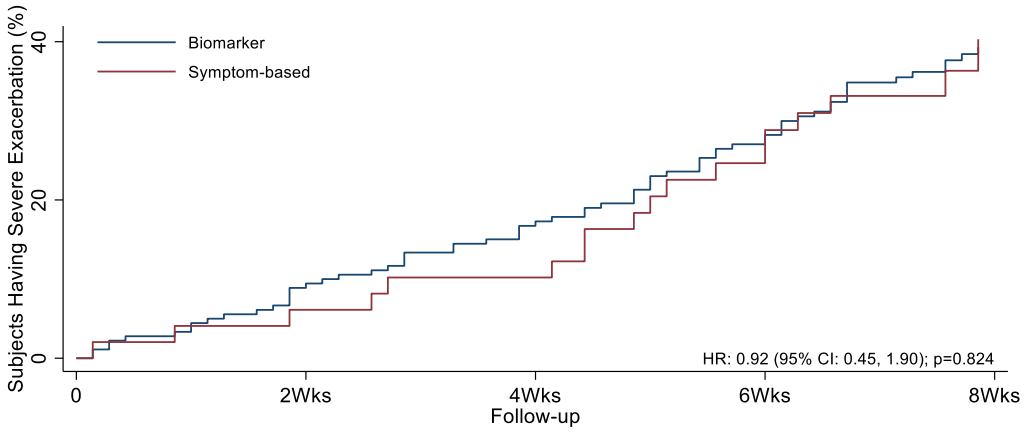


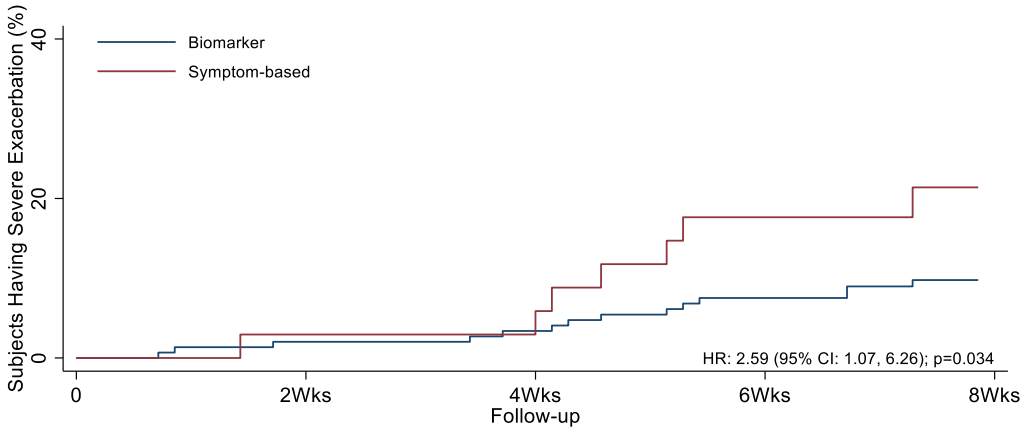
Figure 2. Exacerbation outcome in patients with dissociated symptoms and T2-biomarkers; figure 2a – in the symptom based arm, high symptoms advised treatment increase with no benefit in biomarker low patients; figure 2b – in the symptom based arm – low symptoms advised treatment reduction with a significantly increased exacerbation rate in biomarker high patients

Figure 2a



Number at Risk					
Biomarker	180	164	147	124	0
Symptom-based	49	46	44	36	0

Figure 2b



Number at Risk					
Biomarker	148	145	141	130	0
Symptom-based	34	33	33	27	0

Supplementary Appendix

Factors affecting adherence with treatment advice in a clinical trial of patients with severe asthma.

LIST OF PARTICIPATING CLINICAL CENTRES

NHS Clinical Centres with a dedicated tertiary care in difficult asthma service that recruited to the study

- Belfast Health & Social Care Trust
- Oxford University Hospitals NHS Trust
- Glenfield Hospital, University Hospitals of Leicester NHS Trust
- Wythenshawe Hospital, University Hospitals of South Manchester NHS Trust
- University Hospital Southampton NHS Foundation Trust
- Royal Brompton & Harefield NHS Foundation Hospital
- King's College Hospital NHS Foundation Trust
- Nottingham University Hospitals NHS Foundation Trust
- Sheffield Teaching Hospitals NHS Foundation Trust
- Gartnavel and Stobhill/Glasgow Royal Infirmary Hospitals, Greater Glasgow Health Board
- Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust
- Freemans Hospital, Newcastle upon Tyne NHS Foundation Trust

List of industrial partners in RASP-UK consortium"

- GlaxoSmithKline
- Hoffman la Roche / Genentech Inc
- Amgen
- Astra Zeneca / Medimmune
- Boehringer Ingelheim
- Jannsen
- Circassia
- Vitalograph

Supplementary Table 1a. Recorded reasons for patients not adjusting treatment after an advisory

Reason	Advisory		
	Reduce	Maintain	Increase
Patient directed decisions			
Patient choice	47 (54.0%)	20 (48.8%)	84 (76.4%)
Asthma control deteriorated	10 (11.5%)	6 (14.6%)	2 (1.8%)
Exacerbation	8 (9.2%)	5 (12.2%)	1 (0.9%)
Patient error	4 (4.6%)	4 (9.8%)	4 (3.6%)
External factors interfering with patient directed decision			
Clinician Decision	8 (9.2%)	5 (12.2%)	8 (7.3%)
Logistical error	10 (11.5%)	1 (2.4%)	9 (8.2%)
GP Decision	0 (0.0%)	0 (0.0%)	2 (1.8%)

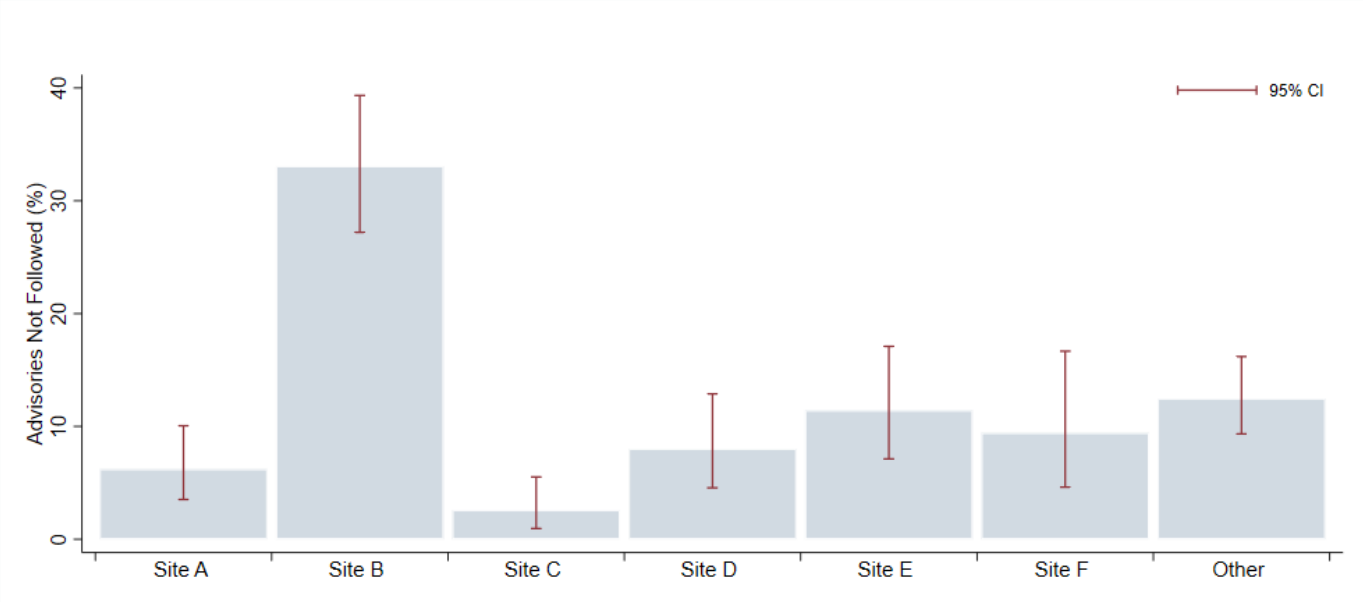
Supplementary Table 1b: Treatment advisories followed in each study arm included in analysis

Treatment Arm	Followed	Refuse
Biomarker		
Reduce	134 (70.5%)	56 (29.5%)
Maintain	821 (96.5%)	30 (3.5%)
Increase	139 (67.1%)	68 (32.9%)
Symptom Assessment		
Reduce	30 (69.8%)	13 (30.2%)
Maintain	206 (97.6%)	5 (2.4%)
Increase	47 (67.1%)	23 (32.9%)
Overall		
Reduce	164 (70.4%)	69 (29.6%)
Maintain	1027 (96.7%)	35 (3.3%)
Increase	186 (67.1%)	91 (32.9%)

Supplementary Table 1c Median % change in type-2 biomarkers between study visits compared to patient self-reported treatment adjustments between study visits for all subjects, including where patients chose not to follow treatment advice. The changes are consistent with expected change in biomarker profile for self-reported treatment

Biomarker	No Change in Treatment	Decreased ICS	Increased ICS	Decreased OCS	Increased OCS
FeNO	0% (-21,36); n=848	14% (-11,46); n=96	-5% (-21, 0); n=11	24% (-11,75); n=47	-17% (-43, 8); n=129
Blood Eosinophils	1% (-20,34); n=823	21% (0,77); n=95	-1% (-15,11); n=12	50% (-13,150); n=42	-47% (-71,-21); n=128
Periostin	1% (-6, 8); n=822	6% (-2,12); n=93	-4% (-13, 2); n=11	8% (-3,21); n=46	-13% (-17,-3); n=127

Supplementary Figure 1. Number of treatment advisories where patients chose not to follow treatment advice by individual clinical centres. Any treatment advisory which was not followed because it was within study protocol (patient on lowest allowed ICS dose, low cortisol preventing prednisolone reduction) or where external barriers intervened in the patient decision to follow study treatment advice (clinician decision to override treatment adjustment or site logistical error) were interpreted as patient following advice to maintain treatment.



Supplementary Table 2 Demographics, medical history, comorbidities, lung function and corticosteroid treatment in the randomised population by Clinical Centre

	A	B	C	D	E	F	Others (6 centres) [n< 20 per centre]	P-value
Number of Patients; N=291	43	44	44	32	31	20	77	
Advisories not followed in study	15 (6.2%)	81 (33.1%)	6 (2.6%)	15 (8.0%)	20 (11.4%)	10 (9.4%)	48 (12.5%)	<0.0001
Advisories not followed (patient choice)	10 (66.7%)	71 (87.7%)	5 (83.3%)	10 (66.7%)	18 (90.0%)	5 (50.0%)	32 (66.7%)	0.0125
Age At Inclusion; N=291	57.7 (14.5)	56.6 (12.7)	55.9 (12.1)	57.8 (11.8)	55.5 (12.0)	54.2 (11.8)	53.8 (14.8)	0.6922
Gender; N=291								0.0217
Female	24 (55.8%)	21 (47.7%)	32 (72.7%)	26 (81.2%)	22 (71.0%)	16 (80.0%)	51 (66.2%)	
Male	19 (44.2%)	23 (52.3%)	12 (27.3%)	6 (18.8%)	9 (29.0%)	4 (20.0%)	26 (33.8%)	
Ethnicity; N=291								0.0028
White	39 (90.7%)	40 (90.9%)	43 (97.7%)	32 (100.0%)	30 (96.8%)	14 (70.0%)	71 (92.2%)	
Ethnic Minority Groups	4 (9.3%)	4 (9.1%)	1 (2.3%)	0 (0.0%)	1 (3.2%)	6 (30.0%)	6 (7.8%)	
BMI (kg/m2); N=290	32.7 (7.7)	30.0 (7.2)	33.5 (6.8)	30.2 (5.1)	33.2 (8.4)	32.1 (4.0)	31.4 (7.8)	0.1682
Smoking Status; N=291								0.9511
Never Smoked	34 (79.1%)	31 (70.5%)	34 (77.3%)	22 (68.8%)	23 (74.2%)	15 (75.0%)	58 (75.3%)	
Ex-Smoker	9 (20.9%)	13 (29.5%)	10 (22.7%)	10 (31.2%)	8 (25.8%)	5 (25.0%)	19 (24.7%)	
Atopic Disease; N=290	32 (74.4%)	35 (79.5%)	28 (63.6%)	18 (56.3%)	22 (71.0%)	13 (68.4%)	53 (68.8%)	0.4252
Hospital admission for asthma (previous year); N=291	3 (7.0%)	12 (27.3%)	6 (13.6%)	7 (21.9%)	9 (29.0%)	4 (20.0%)	14 (18.2%)	0.1681
Emergency room attendance for asthma (previous year); N=291	4 (9.3%)	8 (18.2%)	12 (27.3%)	7 (21.9%)	11 (35.5%)	7 (35.0%)	15 (19.5%)	0.0992
General practice attendance for asthma (previous year); N=291	23 (53.5%)	12 (27.3%)	28 (63.6%)	25 (78.1%)	19 (61.3%)	11 (55.0%)	39 (50.6%)	0.0009
Rescue OCS (Last Year); N=291	2.0 (0.0,3.0)	2.0 (1.0,3.0)	2.0 (1.0,4.0)	2.5 (1.0,4.0)	3.0 (1.0,5.0)	3.0 (1.0,4.0)	2.0 (1.0,4.0)	0.3623
Previous ICU; N=291	9 (20.9%)	10 (22.7%)	12 (27.3%)	6 (18.8%)	6 (19.4%)	4 (20.0%)	15 (19.5%)	0.9683
Ever Been Ventilated; N=62	2 (22.2%)	3 (30.0%)	9 (75.0%)	5 (83.3%)	3 (50.0%)	1 (25.0%)	7 (46.7%)	0.0866
History Of Rhinitis; N=291	38 (88.4%)	27 (61.4%)	28 (63.6%)	23 (71.9%)	21 (67.7%)	12 (60.0%)	52 (67.5%)	0.1114
History Of Eczema; N=291	11 (25.6%)	16 (36.4%)	9 (20.5%)	11 (34.4%)	7 (22.6%)	8 (40.0%)	36 (46.8%)	0.0460
History Of Nasal Polyps; N=291	13 (30.2%)	12 (27.3%)	13 (29.5%)	3 (9.4%)	9 (29.0%)	4 (20.0%)	16 (20.8%)	0.3494
Previous Nasal Surgery; N=291	11 (25.6%)	11 (25.0%)	11 (25.0%)	5 (15.6%)	5 (16.1%)	5 (25.0%)	19 (24.7%)	0.8864
History of Oesophageal Reflux; N=291	29 (67.4%)	24 (54.5%)	27 (61.4%)	14 (43.8%)	22 (71.0%)	12 (60.0%)	47 (61.0%)	0.3508
History of Aspirin Sensitivity; N=291	15 (34.9%)	4 (9.1%)	4 (9.1%)	4 (12.5%)	4 (12.9%)	4 (20.0%)	10 (13.0%)	0.0128

Depression / Anxiety; N=291	12 (27.9%)	12 (27.3%)	19 (43.2%)	9 (28.1%)	14 (45.2%)	8 (40.0%)	17 (22.1%)	0.1195
Hypertension; N=291	16 (37.2%)	12 (27.3%)	14 (31.8%)	14 (43.8%)	9 (29.0%)	5 (25.0%)	22 (28.6%)	0.6744
Osteoporosis / Osteopenia; N=291	9 (20.9%)	10 (22.7%)	12 (27.3%)	4 (12.5%)	13 (41.9%)	4 (20.0%)	13 (16.9%)	0.0980
Osteoarthritis; N=291	13 (30.2%)	9 (20.5%)	11 (25.0%)	4 (12.5%)	12 (38.7%)	6 (30.0%)	22 (28.6%)	0.3136
Hypercholesterolaemia; N=291	7 (16.3%)	5 (11.4%)	10 (22.7%)	3 (9.4%)	7 (22.6%)	8 (40.0%)	13 (16.9%)	0.1003
Diabetes; N=291	6 (14.0%)	5 (11.4%)	3 (6.8%)	2 (6.3%)	5 (16.1%)	4 (20.0%)	8 (10.4%)	0.6389
Cataracts; N=291	7 (16.3%)	5 (11.4%)	3 (6.8%)	2 (6.3%)	5 (16.1%)	3 (15.0%)	8 (10.4%)	0.7030
Obstructive Sleep Apnoea; N=291	2 (4.7%)	2 (4.5%)	4 (9.1%)	1 (3.1%)	6 (19.4%)	2 (10.0%)	0 (0.0%)	0.0085
Ischaemic Heart Disease; N=291	1 (2.3%)	2 (4.5%)	1 (2.3%)	0 (0.0%)	4 (12.9%)	0 (0.0%)	4 (5.2%)	0.1597
Peptic Ulcer; N=291	1 (2.3%)	4 (9.1%)	0 (0.0%)	0 (0.0%)	2 (6.5%)	0 (0.0%)	0 (0.0%)	0.0218
Stroke; N=291	1 (2.3%)	3 (6.8%)	0 (0.0%)	0 (0.0%)	2 (6.5%)	0 (0.0%)	0 (0.0%)	0.0729
Chronic Kidney Disease; N=291	1 (2.3%)	2 (4.5%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	2 (10.0%)	1 (1.3%)	0.2585
Glaucoma; N=291	1 (2.3%)	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (3.2%)	1 (5.0%)	0 (0.0%)	0.4196
Myocardial Infarction; N=291	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	2 (6.5%)	0 (0.0%)	0 (0.0%)	0.0656
% Predicted FEV1; N=291	77.6 (19.9)	78.9 (20.2)	75.6 (19.0)	75.2 (21.9)	75.6 (18.7)	72.1 (17.7)	73.4 (18.3)	0.7507
% Predicted FVC; N=291	91.9 (17.3)	91.5 (16.2)	94.5 (16.4)	89.2 (15.3)	89.6 (12.7)	82.8 (16.5)	91.7 (19.4)	0.2921
FEV_1/FVC; N=291	0.66 (0.10)	0.67 (0.11)	0.63 (0.10)	0.66 (0.16)	0.67 (0.11)	0.70 (0.11)	0.64 (0.12)	0.2813
PEFR (L/min); N=288	409.9 (133.4)	406.0 (150.9)	337.4 (115.9)	346.0 (95.6)	389.0 (114.6)	335.9 (125.5)	369.7 (125.3)	0.0343
Sputum Eosinophils (%); N=119	1.3 (0.3,4.5)	1.7 (0.8,33.0)	1.9 (0.5,13.1)	1.0 (0.3,8.0)	5.4 (0.0,36.2)	. (.,.)	1.3 (0.3,4.8)	
FeNo (ppb); N=291	21 (13,31)	20 (12,28)	14 (11,24)	23 (13,29)	24 (14,38)	20 (17,28)	23 (14,29)	0.0639
Blood Eosinophils (109/L); N=291	0.18 (0.11,0.27)	0.23 (0.10,0.35)	0.26 (0.14,0.35)	0.18 (0.10,0.26)	0.26 (0.12,0.55)	0.23 (0.07,0.29)	0.21 (0.11,0.32)	0.1808
Periostin (ng/ml); N=290	52.2 (13.9)	57.1 (20.2)	54.9 (16.8)	52.0 (10.8)	51.0 (16.5)	49.5 (11.2)	52.1 (17.9)	0.5201
OCS User; N=291	27 (62.8%)	9 (20.5%)	26 (59.1%)	4 (12.5%)	14 (45.2%)	3 (15.0%)	24 (31.2%)	<0.0001
OCS Dose; N=291	5 (0,10)	0 (0,0)	5 (0,8)	0 (0,0)	0 (0,10)	0 (0,0)	0 (0,5)	0.0008
ICS Dose (BDP); N=291	1958 (307)	2431 (849)	2000 (0)	1938 (148)	2645 (994)	2105 (801)	2451 (855)	<0.0001
ACQ7 Score; N=291	2.0 (1.1)	1.5 (1.1)	2.1 (1.1)	1.9 (0.9)	2.1 (1.2)	2.7 (1.4)	1.9 (1.1)	0.0035
AQLQ Total Score; N=281	5.0 (1.3)	5.3 (1.5)	4.5 (1.4)	4.9 (1.2)	4.8 (1.4)	4.2 (1.7)	5.0 (1.3)	0.0546

ER = Emergency Room; ACQ = Asthma Control Questionnaire; OCS = oral corticosteroid; ICS = inhaled corticosteroid; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; PEFR = peak expiratory flow rate

Supplementary Table 3. Univariate associations with all candidate variables used in multivariate analysis

Variable	Description	Categorisation	Univariate association with refusing advisory[a]			
			Overall	Reduce	Maintain	Increase
Gender	Patient gender	Female	Ref	Ref	Ref	Ref
		Male	1.05 (0.70,1.60)	0.97 (0.44,2.14)	1.13 (0.54,2.37)	1.00 (0.49,2.03)
Age	Age at time of study entry (years)	<50	Ref	Ref	Ref	Ref
		50-69	1.22 (0.76,1.94)	1.10 (0.55,2.18)	1.35 (0.56,3.26)	1.27 (0.60,2.68)
		70+	1.02 (0.53,1.97)	0.74 (0.24,2.27)	1.71 (0.60,4.88)	1.24 (0.43,3.59)
Ethnicity	Patient ethnicity	White	Ref	Ref	Ref	Ref
		Ethnic Minority Groups	2.06 (0.95,4.46)	7.85 (2.00,30.86)	1.58 (0.61,4.07)	2.85 (0.80,10.13)
BMI	Body mass index (kg/m^2)	<24.9	Ref	Ref	Ref	Ref
		25-29.9	1.32 (0.68,2.54)	1.81 (0.51,6.49)	0.88 (0.26,2.96)	1.97 (0.70,5.51)
		30+	0.83 (0.44,1.56)	1.25 (0.39,4.07)	0.84 (0.27,2.59)	0.79 (0.29,2.13)
Smoking status	Patient smoking status	Never Smoked	Ref	Ref	Ref	Ref
		Ex-Smoker	1.11 (0.69,1.80)	1.51 (0.80,2.85)	1.33 (0.59,3.00)	0.96 (0.43,2.15)
Years since asthma diagnosis	Time between asthma diagnosis and study entry (years)	<15	Ref	Ref	Ref	Ref
		15-29	1.04 (0.58,1.87)	1.39 (0.54,3.61)	1.22 (0.39,3.84)	0.92 (0.40,2.13)
		30+	1.10 (0.66,1.83)	1.36 (0.66,2.78)	1.18 (0.41,3.36)	1.61 (0.73,3.55)
Asthma hospitalisation	Hospitalisation for asthma in the previous year	No	Ref	Ref	Ref	Ref
		Yes	0.82 (0.49,1.37)	1.00 (0.48,2.08)	1.26 (0.53,2.98)	0.41 (0.13,1.28)
ER visit	Emergency department attendance for asthma in the previous year	No	Ref	Ref	Ref	Ref
		Yes	0.58 (0.32,1.04)	1.42 (0.60,3.36)	0.61 (0.21,1.78)	0.28 (0.09,0.85)
ICU admission	ICU admission for asthma ever	No	Ref	Ref	Ref	Ref
		Yes	1.75 (1.09,2.80)	2.49 (1.26,4.92)	1.08 (0.42,2.75)	1.41 (0.59,3.37)
Comorbidities	Number of comorbidities (oesophageal reflux, depression / anxiety, hypertension, osteoporosis / osteopenia, osteoarthritis, hypercholesterolemia, diabetes, cataracts, obstructive sleep apnoea, ischemic heart disease, stroke, peptic ulcer, chronic kidney disease, glaucoma, myocardial infarction) dichotomised as ≤3 and 4+.	≤3	Ref	Ref	Ref	Ref
		>4	0.82 (0.53,1.25)	0.95 (0.47,1.91)	1.89 (0.91,3.89)	0.71 (0.33,1.52)
Depression / anxiety	Diagnosis of depression / anxiety	No	Ref	Ref	Ref	Ref
		Yes	1.10 (0.68,1.78)	1.35 (0.65,2.79)	1.08 (0.51,2.30)	1.53 (0.66,3.56)
Recent exacerbation	Asthma exacerbation since the previous study visit	No	Ref	Ref	Ref	Ref
		Yes	1.51 (1.02,2.22)	1.80 (0.85,3.80)	1.67 (0.79,3.53)	1.12 (0.56,2.23)
ACQ7 score	Asthma control questionnaire at the time of the study visit	<1.5	Ref	Ref	Ref	Ref
		>1.5	0.94 (0.63,1.39)	2.65 (1.42,4.92)	0.73 (0.35,1.54)	0.63 (0.33,1.22)
ACQ7 difference	Change in asthma control questionnaire from the last study visit	>0.5 Improvement	Ref	Ref	Ref	Ref
		<0.5 Change	0.69 (0.45,1.05)	0.34 (0.16,0.72)	1.09 (0.41,2.86)	0.98 (0.44,2.18)

		>0.5 Deterioration	1.08 (0.69,1.69)	1.00 (0.44,2.31)	1.26 (0.37,4.26)	0.96 (0.38,2.42)
FEV_1 (% Predicted)	FEV1 (%) measurement as the time of the study visit	<60	Ref	Ref	Ref	Ref
		60-79	1.09 (0.63,1.90)	1.02 (0.34,3.03)	2.31 (0.88,6.12)	0.51 (0.21,1.27)
		80+	0.96 (0.55,1.68)	0.64 (0.24,1.73)	1.51 (0.50,4.56)	0.66 (0.28,1.54)
Previous changes	Number of reduce or increase advisories that have previously been followed by the patient	0	Ref	Ref	Ref	Ref
		1	1.67 (1.08,2.59)	1.60 (0.76,3.38)	6.00 (2.17,16.62)	0.72 (0.30,1.75)
		2+	2.07 (1.19,3.62)	2.62 (0.96,7.15)	3.62 (1.05,12.44)	1.41 (0.59,3.36)
Treatment adjustment	Change in medication that would be required if patient was to follow treatment advisory	Maintain Treatment	Ref			
		ICS/OCS Change	11.58 (7.05,19.02)	Ref		Ref
		Add/Remove LAMA	9.95 (4.82,20.53)	0.83 (0.35,1.97)		1.55 (0.54,4.45)
		Add/Remove OCS	24.36 (13.62,43.58)	0.85 (0.18,3.93)		3.23 (1.56,6.69)
		Maintain Treatment	Ref			

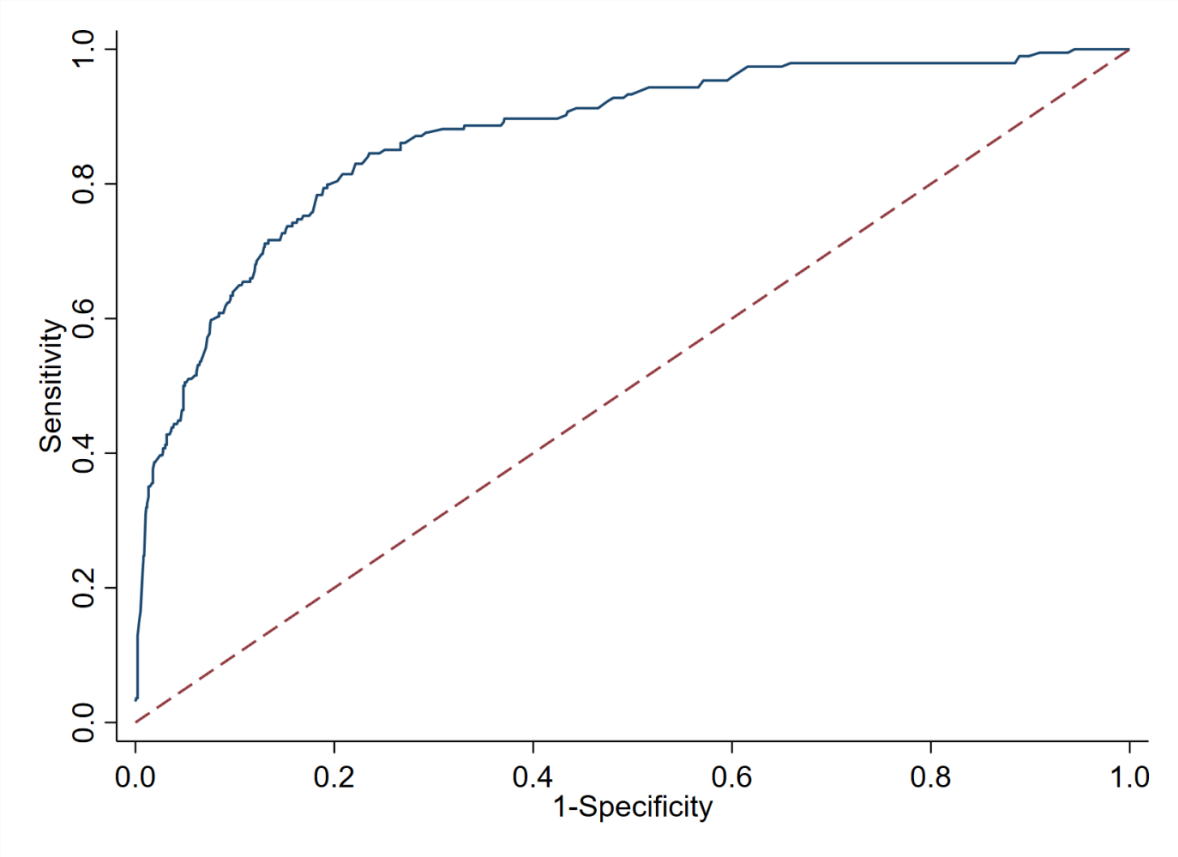
ER = Emergency Room; ACQ = Asthma Control Questionnaire; ICU = intensive care unit; BMI = body mass index

Supplementary Table 4. Comparison of multivariate analysis for reduce and increase advisories

	Reduce (N=233)			Maintain (N=1,062)			Increase (N=277)		
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P-value	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P-value	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P-value
Centre									
Site A	Ref	Ref	.	Ref	Ref	.	Ref	Ref	.
Site B	7.65 (2.15,27.20)	11.42 (2.43,53.61)	0.002	2.68 (0.90,7.92)	3.14 (1.04,9.47)	0.042	17.85 (4.31,73.90)	13.51 (2.29,79.80)	0.004
Site C	0.18 (0.02,1.75)	0.21 (0.02,2.68)	0.231	0.36 (0.07,1.89)	0.35 (0.06,1.98)	0.237	0.66 (0.11,4.08)	0.71 (0.07,6.96)	0.771
Site D	2.97 (0.67,13.09)	4.07 (0.69,23.92)	0.121	0.21 (0.02,1.81)	0.29 (0.03,2.41)	0.251	1.45 (0.18,11.75)	1.67 (0.17,16.44)	0.658
Site E	0.62 (0.12,3.15)	0.46 (0.08,2.70)	0.392	0.79 (0.14,4.37)	0.91 (0.16,4.99)	0.910	4.06 (0.98,16.77)	4.34 (0.70,26.74)	0.114
Site F	1.42 (0.29,6.93)	1.01 (0.22,4.53)	0.992	1.22 (0.29,5.08)	1.47 (0.35,6.11)	0.596	1.78 (0.42,7.63)	0.58 (0.11,3.09)	0.527
Other	1.86 (0.51,6.78)	1.97 (0.45,8.71)	0.370	1.05 (0.31,3.50)	1.05 (0.32,3.46)	0.931	1.93 (0.47,8.02)	1.42 (0.22,9.10)	0.711
Ethnic Minority Groups	7.85 (2.00,30.86)	13.60 (3.53,52.39)	0.000	1.58 (0.61,4.07)	1.98 (0.73,5.37)	0.178	2.85 (0.80,10.13)	3.88 (1.28,11.72)	0.016
Ex-Smoker	1.51 (0.80,2.85)	2.23 (1.01,4.91)	0.047	1.33 (0.59,3.00)	1.36 (0.57,3.20)	0.487	0.96 (0.43,2.15)	0.85 (0.33,2.20)	0.733
ER Visit (Last Year)	2.49 (1.26,4.92)	1.64 (0.67,4.06)	0.282	1.08 (0.42,2.74)	1.13 (0.39,3.21)	0.825	1.41 (0.59,3.37)	1.91 (0.78,4.65)	0.155
ACQ7>1.5	2.65 (1.42,4.92)	3.40 (1.62,7.16)	0.001	0.73 (0.35,1.54)	0.80 (0.38,1.67)	0.554	0.63 (0.33,1.22)	0.88 (0.43,1.79)	0.722
Previous Changes									
0	Ref	Ref	.	Ref	Ref	.	Ref	Ref	.
1	1.60 (0.76,3.38)	1.86 (0.80,4.33)	0.151	6.00 (2.17,16.62)	5.12 (1.86,14.14)	0.002	0.72 (0.30,1.75)	1.35 (0.47,3.87)	0.572
2+	2.62 (0.96,7.15)	4.63 (1.43,14.95)	0.011	3.62 (1.05,12.44)	3.84 (1.06,13.95)	0.041	1.41 (0.59,3.36)	4.61 (1.47,14.47)	0.009
Treatment Adjustment									
Change ICS/OCS Dose	Ref	Ref	.			.	Ref	Ref	.
Change LAMA	0.83 (0.35,1.97)	1.09 (0.34,3.53)	0.887			.	1.55 (0.54,4.45)	1.67 (0.49,5.63)	0.411
Change OCS	0.85 (0.18,3.93)	0.39 (0.13,1.19)	0.097			.	3.23 (1.56,6.69)	3.93 (1.52,10.17)	0.005

ER = Emergency Room; ACQ = Asthma Control Questionnaire; OCS = oral corticosteroid; ICS = inhaled corticosteroid; LAMA = long-acting muscarinic antagonist

Supplementary Figure 2: ROC curve for predicting refusal in all advisories combined



Area under the curve = 0.870 [95%: 0.842, 0899]

Supplementary Table 5. Scoring system and treatment adjustment in both study arms – treatment algorithms were generated automatically by the eCRF software – *biomarker treatment adjustment* (table E5a) – FeNO, blood eosinophil count and serum periostin were measured at each study visit with each biomarker assigned a score of 0, 1 or 2 – the composite biomarker score was generated using the rounded average of the sum of all three biomarker scores. A composite biomarker score of 0 advised treatment reduction, a score of 1 advised maintenance of current treatment and a score of 2 advised treatment increase; *symptom-/risk-based adjustment* (table E5b) – was made using the below algorithm and all therapeutic adjustments calculated automatically and advised through the e-CRF. A score of 0 advised treatment reduction, a score of 1 advised maintenance of current treatment and a score of 2 advised treatment increase. To mirror usual clinical care, patients were not asked to withhold bronchodilator medication prior to study spirometry measurements.

Supplementary Table 5a

Scoring system	**0**	**1**	**2**
FeNO (ppb)	<15	15 - 30	>30
Blood eosinophil count (N/μL)	< 150	150-300	>300
Periostin (ng/mL)	<45	45-55	>55
The **composite biomarker score** was generated using the rounded average of the sum of all three individual biomarker scores e.g. 0 + 1 + 1 = 2/3 = rounded score = 1			

FeNO = fractional exhaled nitric oxide

Supplementary Table 5b

Asthma Control (ACQ- 7)	**Score**
ACQ-7 ≥1.5 and ≥1 change from baseline score *OR* a severe exacerbation since last visit (past 8 weeks at baseline randomisation visit)	2
ACQ-7 is 1.0 to <1.5 OR ACQ ≥1.5 and <1 change from baseline score *AND n*o severe exacerbation since last study visit (past 8 weeks at baseline randomisation visit)	1
ACQ-7 <1.0 *AND* no severe exacerbation since last study visit (prior 8 weeks at baseline randomisation visit)	0

ACQ = Asthma Control Questionnaire

Supplementary Table 6: Comparison of biomarker and symptom based algorithm at each study visit

		Biomarker[b]		
		Score 0	**Score 1**	**Score 2**
Symptoms[a]	**Score 0**	44	169	69
	Score 1	161	596	149
	Score 2	84	224	56

Low Symptoms with dissociated biomarkers

High Symptoms with dissociated biomarkers

[a] Symptoms Score 0 : ACQ-7 <1·0 and no severe exacerbation since last study visit (previous 8 weeks at baseline randomisation visit); Score 1: ACQ-7 is 1·0 to <1·5 or ACQ-7 ≥1·5 and <1 change from baseline score AND no severe exacerbation since last study visit (previous 8 weeks at baseline randomisation visit); Score 2: ACQ-7 ≥1·5 and ≥1 change from baseline score or a severe exacerbation since last study visit (previous 8 weeks at baseline randomisation visit)

[b] FENO, blood eosinophil count, and serum periostin were measured at each study visit with each biomarker assigned a score of 0, 1, or 2. The composite biomarker score was calculated using the rounded average of the sum of all three biomarker scores. FeNO score 0: <15 ppb, score 1: 15-30 ppb, score 2: >30 ppb. Blood eosinophil count score 0: <150 n/µL, score 1: 150-300, score 2: >300. Periostin score 0: <45ng/mL; score 1: 45-55ng/mL; score 2: >55ng/mL.

Supplementary Table 7: Demographics, medical history, comorbidities, lung function and corticosteroid treatment of patients at their first study visit with dissociated symptoms and biomarkers

	High Symptoms / Low or Moderate Biomarkers	Low Symptoms / High or Moderate Biomarkers	P-value
Number of Patients; N=216	133	83	
Age At Inclusion; N=216	53.6 (13.2)	58.0 (12.9)	0.0186
Gender; N=216			0.0056
Female	98 (73.7%)	46 (55.4%)	
Male	35 (26.3%)	37 (44.6%)	
Ethnicity; N=216			0.5397
White	122 (91.7%)	78 (94.0%)	
Ethnic Minority Groups	11 (8.3%)	5 (6.0%)	
BMI (kg/m2); N=59	34.3 (9.7)	28.2 (6.3)	0.0066
Smoking Status; N=216			0.3233
Never Smoked	104 (78.2%)	60 (72.3%)	
Ex-Smoker	29 (21.8%)	23 (27.7%)	
Atopic Disease; N=215	91 (68.9%)	58 (69.9%)	0.8843
Hospital Admissions For Asthma In Last Year (Any); N=216	27 (20.3%)	15 (18.1%)	0.6873
A&E Visits In Last Year (Any); N=216	32 (24.1%)	14 (16.9%)	0.2091
GP Visits For Asthma In The Last Year (Any); N=216	89 (66.9%)	26 (31.3%)	<0.0001
Rescue Courses Of Oral Steroids In The Last Year; N=216	3.0 (1.0,4.0)	2.0 (0.0,3.0)	0.0002
Prior ICU; N=216	33 (24.8%)	11 (13.3%)	0.0402
Ever Been Ventilated; N=44	18 (54.5%)	4 (36.4%)	0.2963
History Of Rhinitis; N=216	87 (65.4%)	59 (71.1%)	0.3864
History Of Eczema; N=216	47 (35.3%)	24 (28.9%)	0.3283
History Of Nasal Polyps; N=216	28 (21.1%)	22 (26.5%)	0.3553
Prior Nasal Surgery; N=216	21 (15.8%)	24 (28.9%)	0.0209
History of Oesophageal Reflux; N=216	83 (62.4%)	45 (54.2%)	0.2335
History of Aspirin Sensitivity; N=216	22 (16.5%)	10 (12.0%)	0.3659
Depression / Anxiety; N=216	50 (37.6%)	16 (19.3%)	0.0045
Hypertension; N=216	45 (33.8%)	26 (31.3%)	0.7025
Osteoporosis / Osteopenia; N=216	33 (24.8%)	9 (10.8%)	0.0116
Osteoarthritis; N=216	45 (33.8%)	15 (18.1%)	0.0119
Hypercholesterolaemia; N=216	23 (17.3%)	15 (18.1%)	0.8837
Diabetes; N=216	17 (12.8%)	8 (9.6%)	0.4824
Cataracts; N=216	12 (9.0%)	11 (13.3%)	0.3269
Obstructive Sleep Apnoea; N=216	9 (6.8%)	3 (3.6%)	0.3252
Ischaemic Heart Disease; N=216	5 (3.8%)	4 (4.8%)	0.7046
Peptic Ulcer; N=216	4 (3.0%)	1 (1.2%)	0.3914
Stroke; N=216	4 (3.0%)	2 (2.4%)	0.7948
Chronic Kidney Disease; N=216	2 (1.5%)	2 (2.4%)	0.6310
Glaucoma; N=216	3 (2.3%)	1 (1.2%)	0.5774
Myocardial Infarction; N=216	2 (1.5%)	0 (0.0%)	0.2617
% Predicted FEV1; N=214	68.9 (18.7)	85.3 (16.4)	<0.0001
% Predicted FVC; N=214	83.2 (16.4)	100.8 (15.8)	<0.0001
FEV1/FVC; N=214	0.66 (0.13)	0.67 (0.11)	0.6729
PEFR (L/min); N=211	343.5 (120.0)	424.7 (116.9)	<0.0001
Sputum Eosinophils (%); N=30	0.2 (0.0,0.6)	4.8 (0.5,25.5)	0.0103
FeNo (ppb); N=216	16 (12,27)	22 (16,32)	0.0084
Blood Eosinophils (109/L); N=216	0.17 (0.08,0.27)	0.21 (0.16,0.33)	0.0012
Periostin (ng/ml); N=216	46.0 (12.4)	58.1 (16.8)	<0.0001
OCS User; N=216	60 (45.1%)	31 (37.3%)	0.2610
OCS Dose; N=216	0 (0,10)	0 (0,5)	0.1854
ICS Dose (BDP); N=216	2130 (879)	2086 (750)	0.7085
ACQ7 Score; N=215	2.8 (1.2)	0.6 (0.2)	<0.0001
AQLQ Total Score; N=56	4.4 (1.5)	6.5 (0.4)	<0.0001

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Statistical analyses

Descriptive statistics are presented as means (SD), medians [IQR] or counts (%) as appropriate. Comparisons between patients who followed all treatment advice during the study and those who refused at least one advisory were made using the t-test (normally-distributed variables), Mann-Whitney U test (non-normally distributed variables) and chi-square test (categorical variables). Initial univariate logistic regression models were used to assess the association for a broad range of demographic and clinical variables which could plausibly impact the patient's decision to follow treatment advisories. A final multivariate model was selected using a modified form of backward selection. Our initial models investigated all advisories combined, however we fitted separate models estimating the probability of following a reduce, maintain or increase advisory. To investigate potential outcome misclassification (due to intentional or unintentional patient misreport) we compared reported medication adjustment with change in T2-biomarkers, which are known to be highly corticosteroid sensitive.

Our initial model investigated all advisories combined, however we fitted separate models estimating the probability of following a reduce, maintain or increase advisory. For simplicity, we aimed to have a consistent set of models across all analyses and so factors that were strongly prognostic for a specific advisory (e.g., increase treatment) were included in all models even if their association was weaker in other analyses. Centre effects were accounted for using fixed-effects and cluster robust standard errors were used to account for the same patients receiving multiple advisories. To improve the interpretability of our results we calculated the estimated marginal means (with 95% confidence intervals) of selected variables, adjusted for potential confounders.

Model discrimination was assessed using receiver operating characteristic (ROC) curves, and the discriminatory performance was quantified using the area under the curve (AUC). We assessed bias

using 10-fold internal cross validation. To investigate potential outcome misclassification (due to intentional or unintentional patient misreport) we compared reported medication adjustment with change in T2-biomarkers, which are known to be highly corticosteroid sensitive. For each treatment advisory we calculated the percentage change in blood eosinophils, FeNO and periostin at the subsequent visit and presented medians (IQR) separately for patients who reported decreasing ICS, decreasing oral corticosteroids (OCS), increasing ICS or increasing OCS. Visits which were preceded by an exacerbation within 14 days were excluded to negate the transient impact of rescue steroids on T2 biomarker levels.

Supplementary analysis compared exacerbation risk among those with a disassociated symptom/biomarker profile. A subgroup of patients with low symptoms and moderate/high biomarkers was identified as was a separate subgroup with high symptoms and moderate/low biomarkers (see supplementary appendix). The outcome was the time to the first exacerbation within the 8-week study period (defined as at least a doubling of treatment with OCS days [for subjects on maintenance OCS] or increase in treatment with OCS to the usual rescue course of oral steroids for ≥3 consecutive days, asthma hospitalisation or parenteral steroid use) with patients considered 'at risk' from the date of the study visit until the day prior to their next study visit (follow-up truncated at 56 days). Comparisons are displayed graphically using Kaplan-Meir plots, and Cox regression models adjusted for age, gender and treatment centre were used to conduct hypothesis tests. Cluster-robust standard errors were used to account for the same patients being included in the analysis multiple times. Analyses were conducted using STATA 16 (StataCorp, Texas, USA).

For simplicity, we aimed to have a consistent set of models across all analyses and so factors that were strongly prognostic for a specific advisory (e.g., increase treatment) were included in all models even if their association was weaker in other analyses. Centre effects were accounted for using fixed-effects and cluster robust standard errors were used to account for the same patients receiving multiple advisories. To improve the interpretability of our results we calculated the estimated marginal means (with 95% confidence intervals) of selected variables, adjusted for potential confounders [7]. Model discrimination was assessed using receiver operating characteristic (ROC) curves, and the discriminatory performance was quantified using the area under the curve (AUC). We assessed bias using 10-fold internal cross validation. To investigate potential outcome misclassification we calculated the percentage change in blood eosinophils, FeNO and periostin and presented medians (IQR) separately for patients who reported decreasing ICS, decreasing oral corticosteroids (OCS), increasing ICS or increasing OCS. Visits which were preceded by an exacerbation within 14 days were excluded to negate the transient impact of rescue steroids on T2 biomarker levels.

Supplementary analysis compared exacerbation risk among those with a disassociated symptom/biomarker profile exacerbations were defined as defined as at least a doubling of treatment with OCS days [for subjects on maintenance OCS] or increase in treatment with OCS to the usual rescue course of oral steroids for ≥3 consecutive days, asthma hospitalisation or parenteral steroid use. Cluster-robust standard errors were used to account for the same patients being included in the analysis multiple times