WHAT MATTERS MOST TO PATIENTS WHEN CHOOSING TREATMENT FOR MILD-MODERATE ASTHMA? RESULTS FROM A DISCRETE CHOICE EXPERIMENT

SUPPLEMENTARY APPENDIX

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1. PRACTICAL Discrete Choice Experiment Study Team

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2. Additional explanation on DCE design and the PAPRIKA method

Details on selection of attributes and levels

Potential attributes and levels for inclusion in the DCEs were identified through a review of the literature, expert consensus and in consultation with participants who had completed the PRACTIAL study before the DCE eligibility date. However, only variables that had been systematically collected during the PRACTICAL study were considered. This was so that the DCE results could be related to measured properties of both treatment regimens. Eleven participants who had completed the PRACTICAL study attended one of three focus groups to explore the most important features of asthma and its management, with particular focus on factors that had been measured within the PRACTICAL study and how the participants may translate them into attributes and levels. The same 11 participants pilot-tested the DCE to check understanding, relevance of selected attributed and levels and time taken to complete the DCE with particular care taken to check agreement with the inherent ranking of attribute levels. Cognitive debriefing was used to enhance feedback. Based on this feedback, iterative changes to the wording of the DCE were made to improve understanding. None of the pilot participants found the DCE to be difficult to understand or unduly burdensome.

Details on the PAPRIKA method

The DCE was based on the PAPRIKA method[1] – an acronym for ***P***otentially ***A***ll ***P***airwise ***R***an***K***ings of all possible ***A***lternatives – as implemented by 1000minds software (www.1000minds.com). The most important features of the method have been explained in the main body of the article. Additional details are provided here – in particular, the method by which the weights, representing the relative importance of the four attributes with respect to choosing between asthma treatments, were derived.

As stated in the methods section of the main article, all DCE methodologies involve participants being asked to choose between two or more hypothetical options which are defined by different combinations of the attributes' levels included in the DCE. The PAPRIKA method involved each participant being asked a series of 'trade-off questions', where each question invited them to choose their preferred asthma treatment from a pair of hypothetical treatments defined on - just two attributes and levels at a time. Each choice required the participant to confront a trade-off between levels of two attributes included for the pair of treatments, where the two other attributes were assumed to be the same for both treatments. An example of a trade-off question appears in Figure 1.

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Such questions (always involving a trade-off between the attributes, two at a time) are repeated with different pairs of hypothetical treatments. Each time the participant answers a question – i.e. ranked a pair of treatments (including potentially ranking them equally) – all other pairs of treatments that could be pairwise ranked by applying the logical property of 'transitivity' are identified and eliminated by the software. For example, as an illustration of transitivity, if a person prefers treatment *X* to treatment *Y* and *Y* to *Z*, then – by transitivity – *X* is also preferred to *Z* (and so is not asked about by the software). Also, each time a person answers a question, the method adapts the selection of the next question based on all of their preceding answers (always one whose answer was not implied by earlier answers); thus, PAPRIKA is a type of *adaptive* DCE. This adaptivity combined with the above-mentioned elimination procedure based on transitivity minimises the number of questions the participant is asked while ensuring they have pairwise ranked all possible treatments defined on two attributes at a time, either explicitly or implicitly (by transitivity).

Derivation of preference weights

The data from which each participant's weights (or 'part-worth utilities') are derived consists of the participant's explicit pairwise rankings (i.e. answers to the trade-off questions) from the DCE. A linear programme based on these pairwise rankings is solved to estimate weights for each level of each attribute that are consistent with the participant's choices. The constraints in the linear programme are key to interpreting the estimated weights, as briefly explained next.

In the theoretical setting of a DCE, a particular hypothetical asthma treatment is conceptualised as a particular combination of levels on the four attributes representing possible treatments. The measure of the preference a person has for a particular treatment – hereinafter referred to as 'utility' – is assumed to be additive across the attributes.[2] Suppose, for example, that *A* and *B* refer to two particular attributes – e.g. "Likelihood of a flare up in your asthma severe enough that you need to see a doctor" and "In an average week you will be short of breath because of asthma" – and they each have three levels (1, 2, 3). Thus, the variable *A*1 represents the utility the participant associates with attribute *A* being at level 1, and so on. With reference to Figure 1 in the main text, when asked, "Which asthma treatment would you choose? … A treatment characterised by *A*2 and *B*2 or another treatment characterised by *A*1 and *B*3?", the participant would choose: (1) the first treatment if utilities $A2 + B2 > A1 + B3$, or (2) the second treatment if $A2 + B2 < A1 + B3$, or (3) "They are equal" if $A2 + B2 = A1 + B3$.

Each such choice made by the participant forms a constraint – corresponding to an inequality or equality (depending on the choice made) – in the linear programme from which the weights for the levels on each attribute (including each attribute's overall weight) are derived. Utility is also

constrained to be non-negative and monotonically increasing in the levels of each attribute; there are no additional functional constraints (such as of diminishing marginal utility). See Hansen and Ombler (2008)[1] for technical details about the linear programme and its solution.

PAPRIKA's application of the transitivity property (as explained above) requires that each attribute's levels have an inherent ranking in terms of people's preferences,[12] i.e. a ranking that would be universally accepted. For example, with respect to the attribute 'likelihood of a flare up', a 5% risk would be assumed to be universally preferred (higher ranked) relative to a 10% risk. In contrast, the two levels for the attribute 'treatment regimen' (i.e. the two randomised treatments in the PRACTICAL study) do not have an inherent ranking because each person's ranking would depend on which therapy they had stated they preferred. Therefore, it was necessary to implement two separate DCEs, identical except that the ranking of the two levels for the 'treatment regimen' attribute were reversed, i.e. for participants who stated they preferred the as-needed therapy this regimen was ranked above the maintenance regimen, and vice versa. After each participant indicated their preferred therapy, they were presented with the appropriate DCE for them.

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3. Information sheets presented to participants

Figure S1: Information presented to participants prior to completing the DCE

Explanation of Terms in the Survey

Reliever inhaler: used when you are getting symptoms of asthma such as breathlessness, wheeze, tight-chested or cough. You may have been on a Ventolin or Respigen inhaler as your reliever before the study. In the study you would have used either Bricanyl (blue) or Symbicort (red) inhaler as your reliever inhaler.

Preventer inhaler: contains a corticosteroid to reduce inflammation. This type of inhaler is normally used regularly twice a day to prevent asthma symptoms and reduce the risk of flare-ups. In the study you may have been using Pulmicort (brown) inhaler twice a day as your preventer. Other preventer inhalers you may have taken before the study are Beclazone (brown) or Flixotide (orange).

Combined preventer and reliever inhaler: In the study, you may have been using Symbicort (red) as a combined preventer and reliever when you had asthma symptoms.

The different inhaler regimens in the study:

Regimen	**What inhalers are given and why?**	**When would I take the inhaler(s)?**	
Symbicort	Symbicort inhaler Combined preventer and reliever This contains: - a beta- agonist to quickly open up the airways - a steroid to reduce airway inflammation	When I have symptoms	
Pulmicort and Bricanyl	Bricanyl inhaler Reliever inhaler This contains a beta- agonist to quickly open up the airways	When I have symptoms	
	Pulmicort inhaler Preventer inhaler This contains a steroid to reduce airway inflammation	Morning and night	

Figure S2: Participant explanation of rationale of a DCE and how to complete the DCE

Explanation of a Conjoint Survey

The survey you're going to do next is called a conjoint survey and is slightly different from a usual questionnaire.

The purpose of this survey is to find out what is important to you from the various features of asthma inhaler regimens.

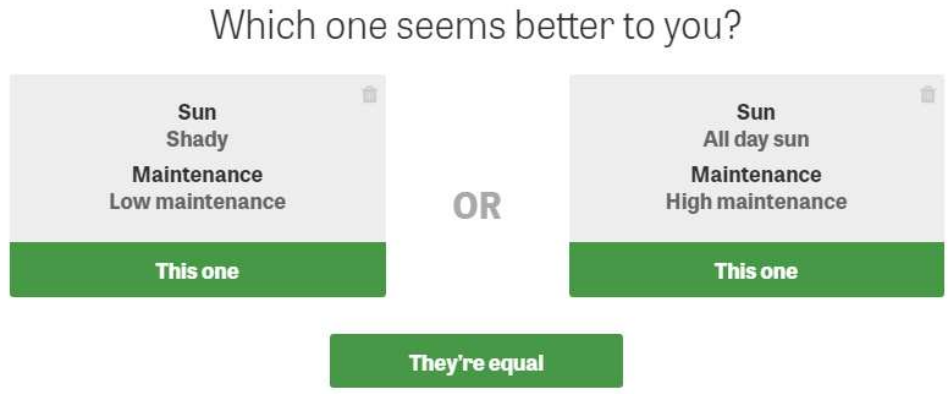
In the survey you'll be shown between 10 and 20 scenarios, it's different each time and for each person. In the scenarios you'll be asked to pick which of the two imaginary asthma inhaler regimens shown you'd prefer or that they are both the same.

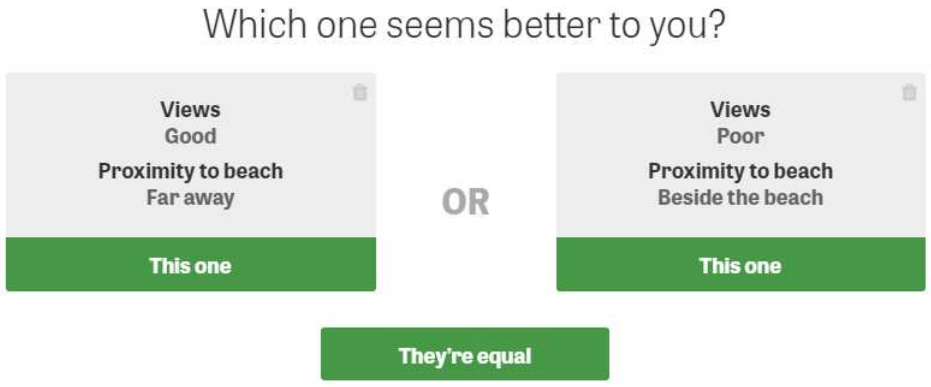
As you go through the scenarios two features of asthma inhaler regimens will be shown and will be different between the two options. For the survey **you'll need to assume that everything else is the same apart** from the two varying features shown on the screen.

You might feel that the scenarios are very similar or the same as ones you've seen before. They will be subtly different and it's the programme trying to work out exactly what is most important to you.

Below are a couple pictures of what the survey will look like, based on some features of buying a house in Wellington.

Please ask if you've got any questions!





4. PRACTICAL study inclusion and exclusion criteria

Table S1: Inclusion and exclusion criteria for the PRACTICAL study

Inclusion criteria	**Exclusion criteria**

• Adults aged 18-75 years.
• Self-report of a doctor's diagnosis of asthma:
• Not used ICS in the 12 weeks prior to entry into the study and:
  ○ asthma symptoms or need for SABA ≥ two occasions in the last 4 weeks, or
  ○ waking due to asthma ≥ once in the last 4 weeks, or
  ○ exacerbation requiring oral corticosteroids in the last 52 weeks
• Used ICS in the 12 weeks prior to entry in the study, and prescribed ICS at low or moderate doses (≤500µg/day fluticasone propionate or small particle formulation beclomethasone diproprionate (QVAR); ≤800 µg/day budesonide; ≤1,000 µg/day beclomethasone diproprionate (Beclazone)), and:
  ○ has partly or well controlled asthma as defined by GINA guidelines, or
  ○ has uncontrolled asthma as defined by GINA guidelines and either poor adherence to ICS and/ or unsatisfactory inhaler technique *
• Willing and able to give informed consent for participation in the trial.
• In the investigator's opinion, able and willing to comply with all trial requirements.
• Willing to allow their GP (and specialist if appropriate) to be notified of participation in the trial.
	• Self-reported use of LABA, leukotriene receptor antagonist, theophylline, anticholinergic agent or cromone as maintenance therapy in the 12 weeks before potential study entry. Nasal corticosteroid therapy is permitted.
	• Self-reported past admission to the Intensive Care Unit (ICU) with life-threatening asthma (representing patients at highest risk of adverse asthma outcomes).
	• Self-reported treatment with oral prednisone or other systemic corticosteroids in the six weeks before potential study entry (representing recent unstable asthma).
	• A home supply of prednisone for use in worsening asthma, as part of a current asthma plan.
	• Self-reported diagnosis of COPD, bronchiectasis or interstitial lung disease.
	• Self-reported greater than 20 pack year smoking history, or onset of respiratory symptoms after the age of 40 years in current or ex-smokers with ≥10 pack year history.
	• Self-reported current pregnancy or breast feeding at the time of enrolment or planned pregnancy within the study period.
	• Unwilling or unable to switch from current asthma treatment regimen.
	• Other illness(es) likely to compromise participant safety or impact on the feasibility of results, at the discretion of the investigator (examples include unstable coronary disease and malignancy).

*Assessment of participant adherence was by patient self-report of inhaler use in the past month at the time of study enrolment.

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5. Additional demographic data and results

Figure S3: Flow of participants

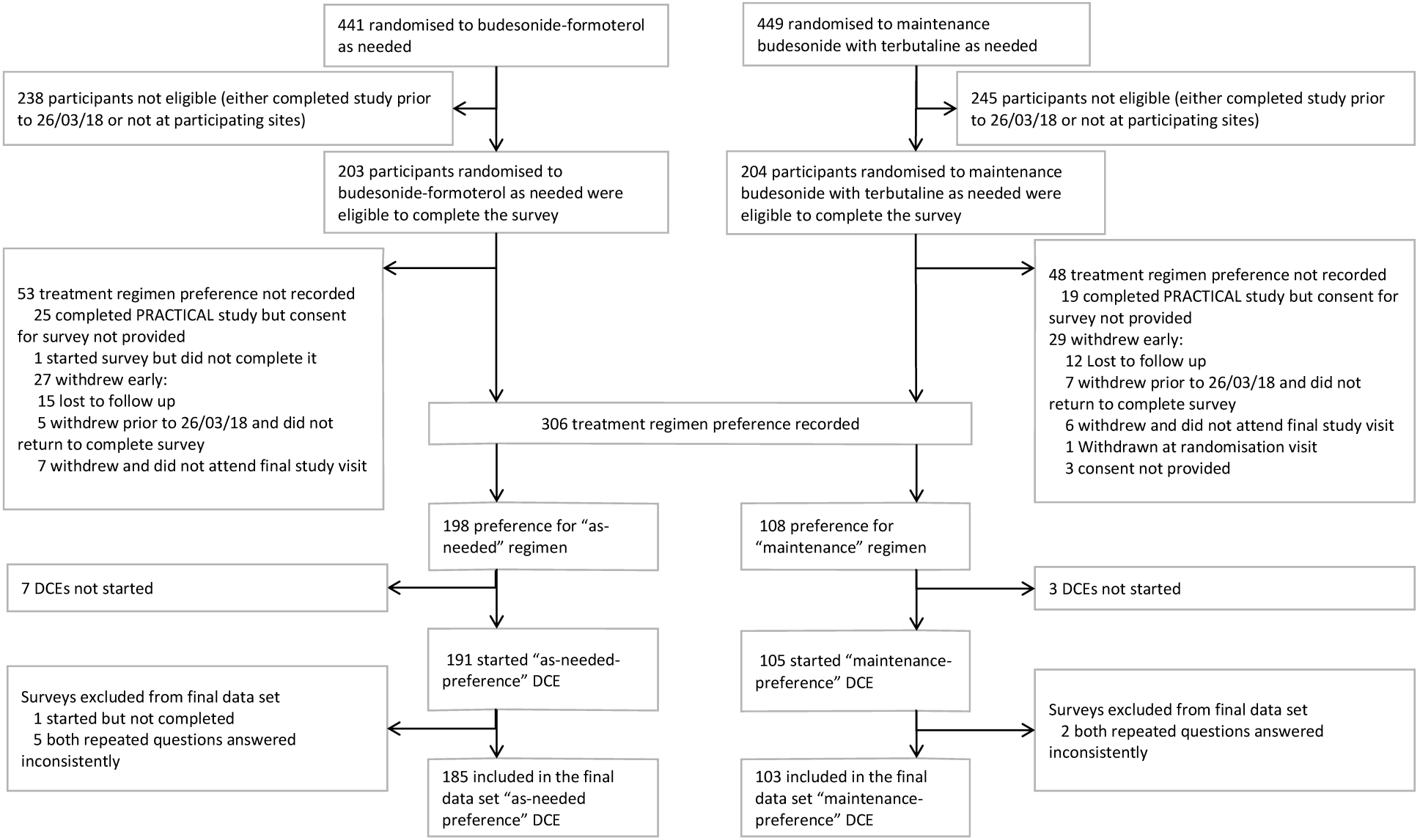

Table S2: As-needed-preference DCE mean attribute preference weight with and without participants who answered consistency questions differently

Attribute	**All surveys, N=190**	**Participants who answered two consistency question differently excluded, N=185**	**Participants who answered one or both consistency questions differently excluded, N=148**
	Mean weight (SD)	Mean weight (SD)	Mean weight (SD)
Treatment regimen	0.24 (0.11)	0.24 (0.11)	0.25 (0.11)
Dose of ICS	0.18 (0.11)	0.17 (0.11)	0.16 (0.10)
Risk of asthma flare up	0.25 (0.09)	0.25 (0.09)	0.26 (0.09)
Shortness of breath in an average week	0.33 (0.12)	0.33 (0.12)	0.34 (0.12)

The table shows the highest preference weight from among the levels for each attribute.

Table S3: Maintenance-preference DCE mean preference weights with and without participants who answered consistency questions differently

Attribute	**All surveys, N=105**	**Participants who answered two consistency question differently excluded, N=103**	**Participants who answered one or both consistency questions differently excluded, N=82**
	Mean weight (SD)	Mean weight (SD)	Mean weight (SD)
Treatment regimen	0.18 (0.12)	0.18 (0.12)	0.18 (0.13)
Dose of ICS	0.19 (0.11)	0.19 (0.10)	0.19 (0.10)
Risk of asthma flare up	0.29 (0.12)	0.30 (0.12)	0.29 (0.12)
Shortness of breath in an average week	0.34 (0.12)	0.34 (0.12)	0.35 (0.13)

The table shows the highest preference weight from among the levels for each attribute.

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Table S4: As-needed-preference DCE: Mean preference weights and attribute ranks by randomised treatment

Attribute	**Budesonide-formoterol as needed, N=125 (68%)**		**Maintenance budesonide, N=60 (32%)**	
	Mean weight (SD)	Rank	Mean weight (SD)	Rank
Treatment regimen	0.25 (0.10)	2	0.22 (0.12)	3
Dose of ICS	0.18 (0.11)	4	0.17 (0.11)	4
Risk of asthma flare up	0.24 (0.09)	3	0.27 (0.08)	2
Shortness of breath in an average week	0.33 (0.12)	1	0.34 (0.12)	1

The table shows the highest preference weight from among the levels for each attribute.

Table S5: Maintenance-preference DCE: Preference weight and attribute rank by randomised treatment

Attribute	**Budesonide-formoterol as needed, N=14 (14%)**		**Maintenance budesonide, N=89 (86%)**	
	Mean weight (SD)	Rank	Mean weight (SD)	Rank
Treatment regimen	0.14 (0.11)	4	0.18 (0.13)	4
Dose of ICS	0.19 (0.09)	3	0.19 (0.11)	3
Risk of asthma flare up	0.34 (0.10)	1	0.29 (0.12)	2
Shortness of breath in an average week	0.33 (0.11)	2	0.34 (0.12)	1

The table shows the highest preference weight from among the levels for each attribute.

Table S6: Characteristics of participants who completed a DCE and who did not

Characteristic	DCE completed, Y=295		DCE not completed, N=112	
	Completed study, N=276 (94%)	Withdrew early, N=19 (6%)	Completed study, N=55 (49%)	Withdrew early, N=57 (51%)
Randomised treatment				
Budesonide-formoterol – no. (%)	138 (50)	6 (32)	31 (56)	28 (49)
Maintenance budesonide – no. (%)	138 (50)	13 (68)	24 (44)	29 (51)
Baseline variables				
Age – yr	45.2 (16.0)	48.9 (19.6)	32.5 (13.1)	30.0 (10.8)
Female sex – no. (%)	153 (55)	11 (58)	30 (55)	28 (49)
Ethnicity – no. (%)				
Asian	16 (6)	1 (5)	4 (7)	6 (11)
NZ European	221 (80)	18 (95)	36 (65)	39 (68)
Maori	21 (8)	0	7 (13)	7 (12)
Other	5 (2)	0	4 (7)	0
Pacific	13 (5)	0	4 (7)	5 (9)
Smoking status – no. (%)				
Current smokers	12 (4)	0	5 (9)	6 (11)
Ex-smokers	71 (26)	5 (26)	16 (29)	15 (26)
Never smokers	193 (70)	14 (74)	34 (62)	36 (63)
Pack years (among ever smokers)	5.6 (5.0) N=83	1.8 (1.9) N=5	4.0 (4.2) N=21	3.7 (4.2) N=21
Age at diagnosis – yr	21.1 (19.6)	20.7 (17.7)	12.5 (10.9)	12.00 (11.9)
Self-reported ICS use in 12 weeks prior to randomisation – no. (%)¥	189 (68)	16 (84)	38 (69)	38 (67)
Self-reported ICS adherence – no.(%)	56.5 (35.9) N=189	60.3 (36.1) N=16	41.5 (37.2) N=38	44.9 (31.6) N=38
Self-reported ICS use ever – no.(%)	236 (86)	17 (89)	40 (73)	42 (74)
End-of-study variables				
Final visit ACQ-5†	0.73 (0.67)	1.20 (1.07)	0.88 (0.88)	1.51 (0.70) N=13
Final visit on treatment FEV1 % of predicted value‡	89.4 (14.7)	89.5 (19.7)	87.4 (14.5) N=52	89.1 (16.3) N=14
Final visit median FeNO – ppb (IQR)	22.5 (15 to 39)	18 (14.5 to 41)	38.5 (26.5 to 56) N=52	38.5 (26 to 56.75) N=14
Participants experiencing ≥1 exacerbation or severe exacerbations – no.(%)	40 (15)	6 (32)	11 (20)	5 (9)

Values are expressed as mean (SD) unless otherwise stated.
¥ Patient-reported adherence to ICSs in the 4 weeks prior to enrolment (% prescribed dose).
† The Asthma Control Questionnaire-5 (ACQ-5) consists of five questions that assess asthma symptoms in the previous week, each of which is scored on a 7-point scale that ranges from 0 (no impairment) to 6 (maximum impairment), and averaged, in which a 0.5-unit change represents the minimal clinically important difference.
‡ Participants received no specific instruction to withhold use of their bronchodilator before measurement of FEV1.[3]

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Table S7: Mean attribute preference weight for participants who withdrew early from the PRACTICAL study

Attribute	**As-needed-preference DCE, N=8** Mean weight (SD)	**Maintenance-preference DCE, N=11** Mean weight (SD)
Treatment regimen	0.24 (0.12)	0.20 (0.12)
Dose of steroid	0.22 (0.14)	0.18 (0.09)
Likelihood of asthma flare up	0.23 (0.06)	0.34 (0.12)
Shortness of breath in an average week	0.31 (0.13)	0.28 (0.12)

The table shows the highest preference weight from among the levels for each attribute.

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6. References

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