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Early View

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Patient-centred composite scores as tools for assesment of response to biological therapy for paediatric and adult severe asthma

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Patient-centred composite scores as tools for assesment of response to biological therapy for paediatric and adult severe asthma.

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Abstract

Background: We have previously developed Core Outcome Measures sets for Severe Asthma (COMSA) by multi-stakeholder consensus. There are no patient-centred tools to quantify response to biologics for severe asthma. We aimed to develop paediatric and adult CompOsite iNdexes For Response in asthMa (CONFiRM) incorporating clinical parameters and patient-reported quality of life (QoL).

Methods: International expert healthcare professionals (HCPs) and patients with severe asthma were invited to: 1) develop consensus levels of clinically relevant changes for each outcome measure within COMSA; 2) use multicriteria decision analysis to develop the CONFiRM scores and 3) assess their internal validity. A separate group of HCPs evaluated CONFiRM's external validity.

Results: Five levels of change for each COMSA outcome were agreed. Severe exacerbations and maintenance oral corticosteroids use were rated as most important in determining both paediatric and adult CONFiRM scores. There was strong agreement between HCPs and patients, although patients assigned greater importance to QoL. The CONFiRM score quantified response to a biological from -31 (deterioration) to 69 (best possible response). Paediatric and adult CONFiRMs had good discriminative ability for a sufficient (AUC≥0.92) and a substantial (AUC≥0.95) response to biologics. Both CONFiRMs demonstrated excellent external validity (Spearman correlation coefficients 0.9 and 0.8 for paediatric and adult respectively ($p<0.0001$)).

Conclusions: We have developed novel patient-centred paediatric and adult CONFiRMs which include QoL measures. CONFiRMs should allow a more holistic understanding of response for the patient and a standardised assessment of the effectiveness of biologics between studies. Further research is needed to prospectively validate CONFiRM scores.

Key words: biological therapy, conjoint analysis, patient-centred, treatment response, severe asthma.

Take home message: CONFiRM is a novel patient-centred measure of overall response to biologics in severe asthma. It shows good external validity and discriminative ability and is likely to be a valuable tool in assessing and comparing effectiveness of biologics in children and adults.

BACKGROUND

Severe asthma affects up to 10% of adults and 2.5% of children with asthma[1] and is associated with impaired quality of life (QoL), frequent severe asthma exacerbations and hospitalisations.[2] Biologics such as omalizumab, dupilumab, tezepelumab, benralizumab, dupilumab, reslizumab and mepolizumab are currently available for patients who remain uncontrolled despite adherence to maximum conventional asthma treatment. The effectiveness of biologics is focused on their reduction in severe asthma exacerbations and oral glucocorticoid-sparing effects, together with other improvements which may include lung function, symptom control and QoL.[1]

Even though biologics represent a major breakthrough, they are burdensome[3] and expensive[4,5]. Hence, they should only be continued if a patient has an adequate response. Patients recognise that not all responses are meaningful[3], however there is no agreed definition of either non-response or adequate response[6]. An expert task force of clinicians has proposed that patients should be classified as non-responders, intermediate responders and super-responders[7] but did not specify which outcome measures should be used in the assessment of the multidimensional nature of severe asthma, or propose cut offs for improvement or deterioration. Other currently available definitions of response to biologics are based on expert opinion, developed only for adult patients, and do not incorporate patient input or standard QoL measures[8,9] which are important to people with severe asthma.[3,10-12] Furthermore, comparing response and identifying biomarkers of response to therapy in current clinical trials is hampered by the different outcome measures and response criteria employed.

To standardise assessment, we have recently developed the Core Outcome Measures sets for paediatric and adult Severe Asthma (COMSA)[12] selected by four stakeholder groups: healthcare professionals (HCPs), patient advocates, pharmaceutical representatives, and regulators. Briefly, both the adult and paediatric COMSA include forced expiratory volume in 1 second (FEV_1), frequency of severe asthma exacerbations[13] and maintenance oral corticosteroid (mOCS) dose. Additionally, the paediatric COMSA includes the Paediatric Asthma Quality of Life Questionnaire[14,15], and Asthma Control Test (ACT)[16,17] or Childhood-ACT[18,19], while the adult COMSA includes the Severe Asthma Questionnaire[20,21] and the Asthma Control Questionnaire-6 [22,23].

In this study we aimed to develop the patient-centred, valid CompOsite iNdexes For Response in asthMa (CONFiRM) to biologics for children and adults. A composite index is important as it facilitates standardised evaluation of an overall patient response, especially when it is heterogeneous. To achieve this, CONFiRMs were developed to incorporate severe asthma exacerbations and other outcome measures selected in the COMSA[12] but weighted according to their relative importance by patient advocates and HCPs. By taking this approach, we addressed the gaps in previous efforts to define response and non-response to biologics, putting patients with severe asthma at the centre.

METHODS

Our approach consisted of four steps to 1) develop consensus levels of clinically relevant changes for each outcome measure in paediatric and adult COMSA[12]; 2) determine relative importance of each COMSA outcome measure for the overall response in the paediatric and adult CONFIRM using the multicriteria decision analysis

(MCDA)[24]; 3) assess internal validity of the CONFiRM scores; and 4) evaluate their external validity. **(Figure 1).** The study was approved by the University of Southampton Ethics and Research Governance Committee (ERGO: 67253).

Participants

Paediatric and adult HCPs from across the globe with extensive experience in managing severe asthma patients on biologics were recruited through professional severe asthma research networks. We also invited people older than 12-years and carers of children older than 5-years with doctor-diagnosed severe asthma, and patient organisation representatives experienced with working with patients with severe asthma receiving biologics. The definition of severe asthma was based on the ERS/ATS joint statement[25]. Patients and patient representatives (hereafter described as patient advocates) were recruited internationally by social media, through clinics (outside of the UK) and patient organisations. One group of HCPs and patients participated in steps 1-3. A separate group of HCPs participated in the step 4. Details of participants training are provided in **Appendix 1.**

Step 1: Develop consensus levels of clinically relevant changes for each COMSA outcome measure

Levels of clinically relevant changes for each outcome measure in COMSA were developed based on published literature[8,13,14,16,21,26-29] where available and agreed by patient advocates and HCPs **(Appendix 2).**

Step 2: Apply MCDA method to develop CONFiRM scores

A MCDA method was used to determine relative importance of each COMSA outcome measure for the overall response in the CONFiRM . Patient advocates and HCPs were presented with pairs of the same two COMSA outcome measures but with different levels of improvement. Other outcomes were assumed to remain the same. Participants were asked to choose which of two scenarios had better response to a biologic **(Figure 2a).** The consistency of each participant's choices was tested by repeating two previously answered scenarios and measuring the time taken to answer each. The relative importance of each COMSA outcome measure was calculated for each participant and were also averaged across all participants. The CONFiRM was developed from these and re-scaled so non-response had a zero scale. This resulted in a maximal response of 69 and a minimal (deleterious) response of -31 **(Appendix 3).**

Step 3: Assess internal validity of CONFiRM scores

Generating paediatric and adult patient profiles

Anonymised patient profiles were selected from 2011 patients[30-36] enrolled in observational studies involving either children or adults with severe asthma treated with mepolizumab, omalizumab, benralizumab, reslizumab or dupilumab **(Table S1)**. A clustering algorithm was used to group together patient profiles with similar patterns of response to biologics **(Appendix 4)**. The number of clusters was set to 50 for the paediatric and adult pools with one patient selected at random from each cluster. Each patient profile had an associated frequency weighting describing number of patients in its cluster.

Rating of overall magnitude of response for each patient profile

Patient advocates and HCPs were asked to assess 50 paediatric and/or 50 adult patient profiles **(Figure 2b)**. They were asked to classify the overall magnitude of response as deleterious, non-response, sufficient-, substantial- or super-response **(Box 1, Appendix 5)).** These reflect working definitions where these exist.[9] The consistency of each participant's ratings was assessed by repeating two randomly selected patient profiles using intraclass correlation coefficient (ICC)[37] **(Appendix 6).**

Calculating total CONFiRM score for each patient profile

The overall CONFiRM score for each paediatric patient profile was calculated using weighting of each outcome measure generated in the paediatric part of step 2. A similar approach was undertaken for the adult profiles.

Validating the CONFiRM scores

For the internal validation of the paediatric and adult CONFiRM, we compared CONFiRM scores (based on step 2 results) for each patient profile with the HCPs and patient advocates rating of their overall magnitude of response (gold standard). Box and whisker plots were generated for each definition of magnitude of response. Kruskal-Wallis test was used to assess differences between each definition.

A receiver operating characteristic (ROC) approach was computed for the sufficient and substantial overall magnitude of response definitions. These definitions were selected as potential clinical decision points for the continuation of a biological therapy with participants' rating of overall response being the gold standard. The analysis was repeated using a bootstrapping methodology, resampling with replacement was used with 1000 replications, to assess for overfitting.[38] Pearson's correlation was used to compare adult CONFiRM with composite definition of response FEOS (FEV_1, exacerbations, OCS, symptoms)[8] and a ROC analysis for comparison with the super-response definition[9].

Stakeholder meeting

Initial results were discussed among patient advocates, HCPs, pharmaceutical representatives, and health regulators.

Step 4: Assess external validity of the CONFiRM scores

New adult and paediatric patients were selected from each cluster generated in step 3 to provide 15 patient profiles for each. A separate group of HCPs was recruited. They assessed patient profiles in terms of magnitude of response **(Appendix 7).** A similar approach as step 3 was used **(Figure 1).** Additionally, participants ranked these new patient profiles from worsening to largest improvement after taking a biological therapy. The ranking was compared with the CONFIRM score for each profile (based on relative importance of outcome measures established in step 2). Participants were blinded to the total CONFiRM score for each patient profile.

Sample size and other statistical considerations

Data were analysed using STATA software version 16.1 (College Station, TX: StataCorp LLC). The study sample size for stages 1-3 was calculated based on precision in estimating change in the response score for each of the five overall magnitude of response definitions. Weighted (by cluster size) and most frequently reported answers (modal response) were reported for each analysis. Sensitivity analyses were undertaken including clusters with more than one patient profile and patient profiles with or without mOCS at baseline. For all analyses, a p-value of <0.05 was considered as statistically significant. See **Appendix 8** for more details.

RESULTS

Step 1: Develop consensus levels of clinically relevant changes for each COMSA outcome measure

The total of 69 [40 (58.0%) HCP; 29 (42.0%) patient advocates] and 72 [40 (55.6%) HCP; 32 (44.4%) patient advocates] individuals participated in the adult and paediatric surveys, respectively **(Table S2).** Consensus was reached for levels of response for each outcome measure **(Tables 1, S3).**

Step 2: Apply MCDA method to develop CONFiRM scores

The same group of participants took part **(Table S4).** Participants assigned the highest relative importance to severe asthma exacerbations and mOCS in both adult and paediatric CONFiRMs **(Table 1, Figure S1).** Weightings were similar for patient advocates and HCP, except that patient advocates rated asthma-specific QoL higher than HCPs **(Figure 3, Tables S5, S6).** Most participants gave the same answer for two repeated patient profiles (54 (81.8%) and 49 (77.8%) participants for paediatric and adult, respectively). Further details in **Tables S7-11, Figure S2**.

Step 3: Assess internal validity of CONFiRM scores

The patient profiles used in this step are summarised in **Table S12.** A total of 146 participants took part: 79 [45 (57.0%) HCPs; 34 (43.0%) patient advocates] reviewed the adult profiles and 67 [44 (65.7%) HCP; 23 (34.3%) patient advocates] reviewed the paediatric profiles. **(Table S13).** Patient advocates and HCPs appeared to classify responses for each patient profile similarly **(Figure S3)**. Agreement on assigned overall magnitude of response for repeated profiles was moderate for individual participants for the adult patient profiles **(Table S14).** Agreement was also moderate for HCP but very low for patient advocates for the paediatric patient profiles.

There was a clear relationship between the CONFiRM scores for each patient profile and participants' rating of overall magnitude of response (**Figure 4, Table S15)**. Similar results were found for patient profiles where mOCS was not used at baseline **(Figure S4)**.

The composite measures had excellent discriminative ability for substantial response as compared with less than substantial response for paediatric (ROC area under the curve (AUC) 0.99 (95% CI 0.99, 0.99)) and adult CONFiRM (0.95 (95% CI 0.95; 0.96)). This was also the case for sufficient response **(Figure S5-S6)** plus for HCPs and patient

advocates, whether on or off mOCS at baseline, and in the additional bootstrap analysis to minimise impact of overfitting **(Table S16).**

There was high level of correlation between the adult CONFiRM and FEOS[8] using 0.75 and 1.5 ACQ-5 cut offs (r=0.93 and r=0.92 respectively, both p<0.001) **(Figure S7).** The adult CONFiRM also showed good discrimination for super-responders as per the Delphi definition[9] (AUC 0.93 (95 CI% 0.92-0.94), p<0.001) **(Figure S8).**

A total of 75 participants attended the stakeholder meetings including 48 (64.0%) HCPs, 19 (25.3%) patient advocates, 5 (6.7%) pharmaceutical representatives, 2 (2.7%) health regulators and one (1.3%) representative from the 1000minds team. Several comments for improvement of the CONFiRM tools were suggested and implemented **(Table S17).**

Step 4. Assess external validity of the CONFiRM scores

A total of 15 new cases were generated for both the paediatric and adult surveys **(Table S18).** Total CONFiRM score was calculated for each profile. A new group of 97 participants from 28 countries took part in assessing overall magnitude of response for these profiles **(Table S19).** ICC for repeated profiles were 0.59 and 0.65 for paediatric and 0.12 and 0.70 for adult profiles demonstrating mostly moderate agreement **(Table S20).**

Again, there was a clear relationship between the CONFiRM's score for each patient profile and overall magnitude of change **(Figure 5, Table S21)** as we found in step 3 (**Figure 4**)**.** Similar results were found for adult patient profiles where mOCS was not used at baseline **(Figure S9).** Additionally, the composite measures had excellent discriminative ability for both substantial and sufficient responses **(Figure S10).** Lastly, ranking of 15 cases in order of improvement after taking a biologic was positively correlated with the CONFiRM score (Spearman r=0.9 and 0.8 for paediatric and adult patient profiles respectively (p<0.0001) **(Figure 6).**

DISCUSSION

We have developed the patient-centred CompOsite iNdex For Response in asthMa (CONFiRM) to biologics for children and adults. We employed a rigorous methodology to quantify the overall response to biologics, and by involving 147 expert HCPs and patient advocates from more than 25 countries these should be internationally applicable. This study builds on the recently developed COMSA[12] to holistically assess the response for an individual patient. This is important given the heterogeneity of response for different outcomes to biologics that we highlighted in this study. The relative importance of outcome measures assigned by HCPs and patient advocates were similar; however, patients rated asthma-specific QoL more than HCPs as seen previously.[3,11] Internal validation of the CONFiRM was demonstrated based on expert clinicians' and patient advocates' classification of the treatment response in patient profiles. Paediatric and adult CONFiRM have good discriminatory power for both a sufficient and substantial response to biologics. Lastly, external validity of the CONFiRMs provided similar results as internal validation.

Other composite definitions of response to biologics such as FEOS[8] and the super-responder[9] definition were developed only by clinicians and only for adult patients. This contrasts with CONFiRMs' in-depth public and patient involvement throughout the development, conduct and interpretation of the findings. People with severe asthma have the greatest stake in identifying which treatment 'works' for them and by excluding their voices in defining response, the research community risks overlooking factors which matter most to them such as QoL. FEOS[8] was created by a Spanish group of clinicians using a similar MCDA approach. Even though our adult CONFiRM score is highly correlated with FEOS, we suggest that CONFiRM should be preferred as it is patient-centred, includes QoL and divides change in FEV_1 according to the recent ERS/ATS practice parameter.[26] The super-responder definition was developed by clinicians through a Delphi process and includes minor and major criteria.[9] CONFiRM had good discriminatory power for the published Delphi super-response definition but this represents an extreme response only seen in a minority of patients.

Strengths and limitations

The overall magnitude of response definitions are based on the COMSA outcome measures that were selected by four stakeholder groups after assessing their validity, reliability and availability in clinic.[12] We involved a large number of participants from more than 25 countries to include diverse experiences of clinical management of severe asthma patients on biologics and lived experience of participants who are taking or have previously taken biologics. Patient profiles were developed from large observational studies with different biologics to capture diverse patterns of response. A transparent and robust approach was used, including the MCDA methodology.[24] Further, the CONFiRM is a continuous score which provides greater granularity as a quantitative description of improvement for each patient, rather than just a simple categorical score. Our simultaneously developed paediatric and adult CONFiRM showed similar results providing a degree of replication. We have reported internal validation data for both HCPs and patient advocates that showed excellent discriminative ability for substantial and sufficient response even when a bootstrapping approach was taken to minimise overfitting. Lastly, an external validation replicated these results.

We acknowledge some limitations. Step 3 and 4 patient profiles were developed from patients from the same, small number of European countries; other countries may have different initiation criteria for biologics or mOCS. Although we received responses from adolescents and young adults, most paediatric profiles were rated by patient advocates (18+ years) who were diagnosed with asthma in childhood. Also, for the relative importance of outcome measures, we assumed that ACT and C-ACT would have the same weightings. ICC for some repeated cases were poor for patient advocates suggesting that they interpreted responses more variably than clinicians. The score ranges for each overall magnitude of response definitions should be prospectively validated in further studies including looking at association between patient's baseline clinical condition and CONFIRM score and association between overall changes after taking a biologic based on Likert scale for individual patients. There is also a ceiling effect such that patients with compromise in only one COMSA outcome (e.g. exacerbations) would have less potential to benefit compared to those with compromise across multiple outcomes (e.g. exacerbations, mOCS,

uncontrolled symptoms and poor lung function). Both the magnitude of the improvement and the outcome are important here for the patient.

Clinical and policy implications, future work and conclusions

The composite response index is especially important as not all patients with severe asthma respond to high-cost biologics. The overall magnitude of response definitions with their corresponding scores should assist HCPs in assessing whether a biologic has provided a substantial benefit to patients. Our data provides preliminary score ranges for different magnitudes of response. This should inform shared-decision with the patient to continue a biologic or pursue an alternative approach. Further studies should confirm the appropriate time for assessing response, the scores' external validity, determine the ranges associated with a sufficient and substantial response and compare improvements in CONFiRMs with improvements in Quality-Adjusted Life Years (QALYS). We also envisage that use of the CONFiRMs in clinical trials, registries and clinical practice would be facilitated by developing a web-based tool and a downloadable calculator. The widespread use of these patient-focused consensus criteria of response should help in assessing the effectiveness of novel therapies, enabling head-to-head comparisons of different biologics and supporting the calculation of sample size for future clinical trials. Further discussions with policy makers and regulatory bodies are needed on how best to use these composite scores to improve the assessment of biologics for severe asthma. In conclusion, the development of the patient-centred CONFiRM scores to quantify response to biologics for paediatric and adult severe asthma will enable the evaluation of response to therapy in a valid, standardised manner. This should improve the quality of future research and clinical practice ensuring patients receive the best treatment.

Contributions

EK, GR: Conceptualization, Methodology; GR, EK: Statistical analysis; EK: Drafting of the original manuscript; All authors reviewed, edited and approved the final version of the manuscript.

Conflict of interest

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Tables.

Box 1. Working definitions of overall magnitude of response used in the study.

- **Deleterious (negative) response:** a worsening in asthma after starting the biological therapy.
- **Non-response:** no change in asthma or an improvement in asthma that is less than the sufficient response.
- **Sufficient response or Minimal Clinical Important Difference (MCID):** the smallest improvement in asthma that a patient would consider as important and would help in further doctor-patient decision-making.
- **Substantial response:** an improvement in asthma that a patient would consider as being 'big enough' to justify the use of biological therapy for their asthma. It is expected that a substantial response would be larger than sufficient response but smaller than super-response.
- **Super-response:** an improvement in asthma to such a level that asthma can be considered as well-controlled or in (induced) remission; for example, no severe exacerbations, no need for maintenance oral corticosteroids and in some cases even (almost) no symptoms and normal lung function. Hence, this improvement would be larger than the sufficient and substantial response to biological therapy.

These definitions were selected and refined by 52 participants from four stakeholder groups of the 3TR Respiratory Working Group **(Appendix 5).**

Table 1. CompOsite iNdex For Response in asthMa (CONFiRM) in children and adults

A. Paediatric CONFiRM

	Select	Points
Severe asthma exacerbations[8]: change relative to previous 12 months		
Increase#	☐	-10
No change##	☐	0
Reduction <50%	☐	9
Reduction from 50% to < 100%	☐	17
100% reduction	☐	23
Maintenance OCS dose for asthma:[8] change relative to baseline		
Increase*	☐	-8
No change**	☐	0
Reduction <50%	☐	7
Reduction from 50% to < 100%	☐	13
Complete withdrawal***	☐	18
ACT: change relative to baseline		
Decrease ≥ 2 points[27]	☐	-5
No change (increase <2 or decrease < 2 points)	☐	0
Increase ≥2 points and total score ≤19[16]	☐	4
Increase ≥2 points and total score 20 to <23[27]	☐	8
Increase ≥ 2 points and total score ≥ 23	☐	11
On treatment FEV_1◊: change relative to the predicted FEV_1 value at baseline		
Decrease ≥10%[26]	☐	-4
No change (decrease <10% or increase <10%)	☐	-0
Increase from 10% to <15%	☐	4
Increase from 15% to <20%	☐	7
Increase ≥20%	☐	9
PAQLQ: change relative to baseline		
Decrease ≥ 0.5 points[14]	☐	-4
No change (increase < 0.5 or decrease < 0.5 points)	☐	0
Increase ≥ 0.5 points and total score < 5	☐	2
Increase ≥ 0.5 points and total score 5 to < 6	☐	5
Increase ≥ 0.5 points and total score ≥ 6	☐	8
Total score	☐	

B. Adult CONFiRM

	Select	Points
Severe asthma exacerbations:[8] change relative to previous 12 months		
Increase#	☐	-10
No change##	☐	0
Reduction <50%	☐	9
Reduction from 50% to < 100%	☐	16
100% reduction	☐	22
Maintenance OCS dose for asthma:[8] change relative to baseline		
Increase*	☐	-8
No change**	☐	0
Reduction <50%	☐	8
Reduction from 50% to < 100%	☐	14
Complete withdrawal***	☐	19
SAQ: change relative to baseline		
Decrease ≥ 0.5 points[21]	☐	-5
No change (increase <0.5 or decrease <0.5 points)	☐	0
Increase ≥0.5 points and total score <5	☐	4
Increase ≥0.5 points and total score 5 to <6	☐	7
Increase ≥0.5 points and total score ≥6	☐	10
ACQ-5: change relative to baseline		
Increase ≥0.5 points[28]	☐	-4
No change (increase <0.5 or decrease <0.5 points)	☐	0
Decrease ≥0.5 points and total score >1.5[29]	☐	3
Decrease ≥0.5 points and total score from >0.75 to 1.5	☐	6
Decrease ≥0.5 points and total score ≤0.75[29]	☐	9
On treatment FEV_1: change relative to the predicted FEV_1 value at baseline		
Decrease ≥10%[26]	☐	-4
No change (decrease <10% or increase <10%)	☐	0
Increase from 10% to <15%	☐	4
Increase from 15% to <20%	☐	6
Increase ≥20%	☐	9
Total score	☐	

Calculation of CONFIRMs scores: Points are assigned for the change in each COMSA outcome measure. Higher scores indicate better response to a biologic; the range of responses runs from -31 (deleterious response) to 69 (best possible response).

For each outcome, five levels of change are presented: worsening, no change, small change, moderate change and large change. Relative weights were converted into points for each core outcome measure.

Severe asthma exacerbations are defined as per ERS/ATS guideline.[13] Maintenance oral corticosteroid use is defined as daily or alternate day use of oral corticosteroids. C-ACT is for children 6-11 years and ACT is for children from 12-18 years. To avoid completing the step 3 twice, we assumed that ACT and Childhood-ACT have the same weighting in the composite.

*Or if the patient was not receiving maintenance OCS and started the drug. **Or if the patient was not receiving maintenance OCS and remained without them. ***Low dose of maintenance OCS for adrenal insufficiency should be treated as withdrawal of maintenance oral corticosteroid.[8]

#Or if the patient was free of severe asthma exacerbations. ##Or if the patient was free of asthma exacerbations and continued to have no severe asthma exacerbations.[8]

◊Change in on treatment FEV_1 is calculated as [(follow up FEV_1 minus baseline FEV_1 divided by predicted FEV_1 value) x 100].[26] Percent predicted FEV_1 is being used rather than z-score only because this was more comprehensible to patient advocates participating in the project.

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; FEV_1, forced expiratory volume in 1 second; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; OCS, oral corticosteroids; SAQ, Severe Asthma Questionnaire.

Figure legends

Figure 1. Flow diagram of the study. COMSA, Core Outcome Measures for Severe Asthma; CONFiRM, CompOsite iNdex For Response in asthMa; HCP, healthcare professionals; MCDA, multicriteria decision analysis; PP, patient profiles. Words in italic indicate differences between steps.

Figure 2. Example of patients. A. Scenarios generated by 1000minds in step 2 . B. Patient profiles presented in steps 3 and 4. Similar scenarios and patient profiles were presented for the paediatric surveys. Emoji were used to help participants in rating the scenarious. Severe asthma exacerbations are defined as per ERS/ATS guideline.[13] Maintenance (regular) oral corticosteroid use is defined as daily or alternate day use of oral corticosteroids. ACQ, asthma control questionnaire; COMSA, Core Outcome Measures for Severe Asthma; OCS, oral corticosteroids; FEV_1, percent predicted forced expiratory volume in 1 second; SAQ, severe asthma questionnaire.

Figure 3. Maximal weights for each core outcome measure in the CONFIRMs. A. Paediatric CONFiRM. B. Adult CONFiRM. Spider plots describe the maximal mean weight assigned to each COMSA[12] outcome measure. The panel assumed that ACT and Childhood-ACT have the same weighting in the paediatric CONFIRM. Severe asthma attacks are defined as per ERS/ATS guideline.[13] Maintenance oral corticosteroid use is defined as daily or alternate day use of oral corticosteroids. ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; CONFiRM, CompOsite iNdex For Response in asthMa; FEV_1, percent predicted forced expiratory volume in 1 second; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; OCS, oral corticosteroids; SAQ, Severe Asthma Questionnaire.

Figure 4. CONFiRM score in step 3 (internal validation). A. Paediatric CONFiRM. B. Adult CONFiRM. Magnitude of response was most frequently selected (modal) by healthcare professionals and patient advocates for 50

patient profiles. Definitions of overall magnitude of response used in the study are presented in the box 1. Total score for these patient profiles was calculated based on weights for each outcome measure assigned in step 2 . Analysis weighted by case frequency. CONFiRM score for each patient case represented by box and whisker plots (box: median with 25th and 75th centiles; lines represent 2.5 to 97.5 centiles). The CONFiRM scores for each overall magnitude of change (deleterious to super-response) were significantly different for both the paediatric (Kruskal-Willis $\chi2$= 2623.1, p<0.0001; $\chi2$=2506.5, p<0.0001; $\chi2$= 2657.1, p<0.0001 for all participants, patient advocates and HCPs respectively) and adult CONFiRMs ($\chi2$= 2974.7, p<0.0001; $\chi2$= 2854.3, p<0.0001; $\chi2$= 3216.3, p<0.0001). CONFiRM, CompOsite iNdex For Response in asthMa.

Figure 5. CONFiRM score in step 4 (external validation). A. Paediatric CONFiRM. B. Adult CONFiRM. Magnitude of response was most frequently selected (modal) by healthcare professionals for 15 patient profiles. Definitions of magnitude of response used in the study are presented in the box 1. Total score for these patient profiles was calculated based on relative weights for each outcome measure assigned at step 2. Analysis weighted by case frequency. CONFiRM score for each patient case represented by box and whisker plots (box: median with 25th and 75th centiles; lines represent 2.5 to 97.5 centiles). CONFiRM scores for each overall magnitude of change (deleterious to super-response) were significantly different for both the paediatric (Kruskal-Willis $\chi2$= 502.7, p<0.0001) and adult CONFiRM tools ($\chi2$= 648.5, p<0.0001). CONFiRM, CompOsite iNdex For Response in asthMa. Similar results were found for adult patient profiles where mOCS was not used at baseline (**Figure S11**).

Figure 6. Ranking of the 15 patient profiles in order of improvement on biologics from 1st (worsening) to 15th (largest improvement) in stage 4. A. Paediatric patient profiles. B. Adult patient profiles. Ranks for each patient profile are represented by box and whisker plots (box: median with 25th and 75th centiles; lines represent 2.5 to 97.5 centiles). Weighting of each patient profile in the dataset was calculated based on the number of patient profiles per cluster. Both CONFiRMs demonstrated excellent external validity (Spearman correlation coefficients r=0.9 and 0.8 for paediatric and adult patient profiles respectively (p<0.0001)

Aim

Development and validation of the

CompOsite iNdex For Response in asthMa (CONFiRM) to biologics

Methods

HCP with experience in managing patients on biologics

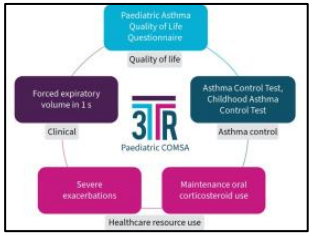
Paediatric and adult patients with severe asthma

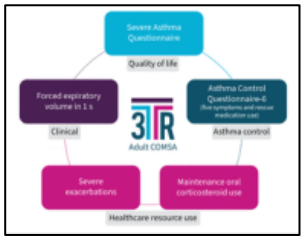
Outcome measures			Data		Change		Changes seen in a patient one year after biological treatment
COMSA		Characteristics	Before	After 1 year therapy	Absolute	Percent	
Asthma control (ACQ-6)	ACQ-6	• Higher score= worse • Range=0-6 points • Score of 1.5 or more indicates poor control	4.8	2.6	↓ 2.2 points	↓ 46%	• Woken by asthma during night – improved from *'A great many times'* to *'A few times'* • Asthma symptoms at night – improved from *'Severe symptoms'* to *'Moderate symptoms'* • Activity limitations – improved from *'Extremely limited'* to *'Slightly limited'* • Shortness of breath – improved from *'A very great deal'* to *'A great deal'* • Wheeze – improved from *'A moderate amount of the time'* to *'Hardly any of the time'*
	Reliever medication use	• Higher score= worse • Range=0-6 points	1	0	↓ 1 point	↓ 100%	• Reliever medication use – improved from *'1 - 2 puffs/inhalations most days'* to *'None'*
Quality of life	SAQ	• Higher score= better • Range=1-7 points	3	3.5	↑ 0.5 points	↑ 15%	• Social, personal & leisure life – improved from *'Difficult'* to *'Moderately difficult'* • Depression, irritable or anxious – no change - *'Difficult'* • Tired, appearance, medicine side effects – improved from *'Difficult'* to *'Moderately difficult'*
	SAQ global	• Higher=better • Range= 0-100	37	43	↑ 7 points	↑ 18%	• Overall quality of life – improved from *'Somewhat bad/bad'* to *'Somewhat bad'*
Lung function, (FEV$_1$ % predicted)		• ≥ 80% =normal	52	57	↑ 5% points	↑ 10%	• Lung function – improved by a very small amount from initially low lung function
Severe asthma attacks, number per year		• None = better	6	2	↓ 4 attacks	↓ 67%	• Severe asthma attacks – improved from 6 attacks a year to 2
Regular oral steroids, prednisolone dose (mg)		• None = better	0	0	No change		• Regular oral steroids for asthma – not treated with them

Notes: getting better; no change or negligible change; getting worse.

Patient profiles created from large clinical trials with different biologics

Based on best validated COMSA outcome measures e.g. clinical parameters and measure of quality of life

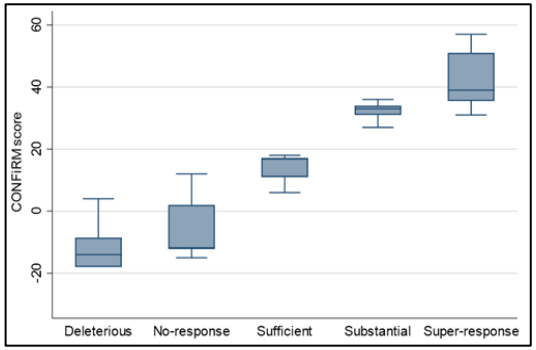




Results

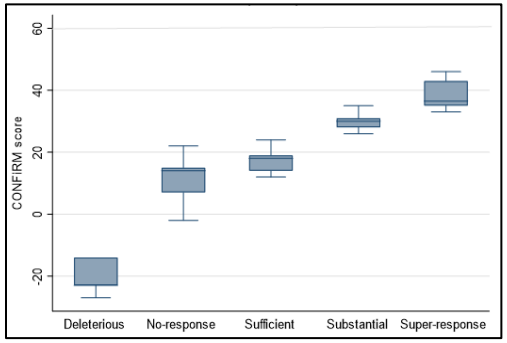
Paediatric CONFIRM

	Select	Points
Severe asthma exacerbations[§]: change relative to previous 12 months		
Increase[#]	☐	-10
No change[##]	☐	0
Reduction <50%	☐	9
Reduction from 50% to < 100%	☐	17
100% reduction	☐	23
Maintenance OCS dose for asthma:[§] change relative to baseline		
Increase*	☐	-8
No change**	☐	0
Reduction <50%	☐	7
Reduction from 50% to < 100%	☐	13
Complete withdrawal***	☐	18
ACT: change relative to baseline		
Decrease ≥ 2 points[27]	☐	-5
No change (increase <2 or decrease < 2 points)	☐	0
Increase ≥2 points and total score ≤19[16]	☐	4
Increase ≥2 points and total score 20 to <23[27]	☐	8
Increase ≥ 2 points and total score ≥ 23	☐	11
On treatment FEV$_1$[§]: change relative to the predicted FEV$_1$ value at baseline		
Decrease ≥10%[26]	☐	-4
No change (decrease <10% or increase <10%)	☐	-0
Increase from 10% to <15%	☐	4
Increase from 15% to <20%	☐	7
Increase ≥20%	☐	9
PAQLQ: change relative to baseline		
Decrease ≥ 0.5 points[14]	☐	-4
No change (increase < 0.5 or decrease < 0.5 points)	☐	0
Increase ≥ 0.5 points and total score < 5	☐	2
Increase ≥ 0.5 points and total score 5 to < 6	☐	5
Increase ≥ 0.5 points and total score ≥ 6	☐	8
Total score		



Adult CONFIRM

	Select	Points
Severe asthma exacerbations:[§] change relative to previous 12 months		
Increase[#]	☐	-10
No change[##]	☐	0
Reduction <50%	☐	9
Reduction from 50% to < 100%	☐	16
100% reduction	☐	22
Maintenance OCS dose for asthma:[§] change relative to baseline		
Increase*	☐	-8
No change**	☐	0
Reduction <50%	☐	8
Reduction from 50% to < 100%	☐	14
Complete withdrawal***	☐	19
SAQ: change relative to baseline		
Decrease ≥ 0.5 points[21]	☐	-5
No change (increase <0.5 or decrease <0.5 points)	☐	0
Increase ≥0.5 points and total score <5	☐	4
Increase ≥0.5 points and total score 5 to <6	☐	7
Increase ≥0.5 points and total score ≥6	☐	10
ACQ-5: change relative to baseline		
Increase ≥0.5 points[28]	☐	-4
No change (increase <0.5 or decrease <0.5 points)	☐	0
Decrease ≥0.5 points and total score >1.5[29]	☐	3
Decrease ≥0.5 points and total score from >0.75 to 1.5	☐	6
Decrease ≥0.5 points and total score ≤0.75[29]	☐	9
On treatment FEV$_1$: change relative to the predicted FEV$_1$ value at baseline		
Decrease ≥10%[26]	☐	-4
No change (decrease <10% or increase <10%)	☐	0
Increase from 10% to <15%	☐	4
Increase from 15% to <20%	☐	6
Increase ≥20%	☐	9
Total score		



CONFIRM: standardised assessment of the effectiveness of biologics for asthma.

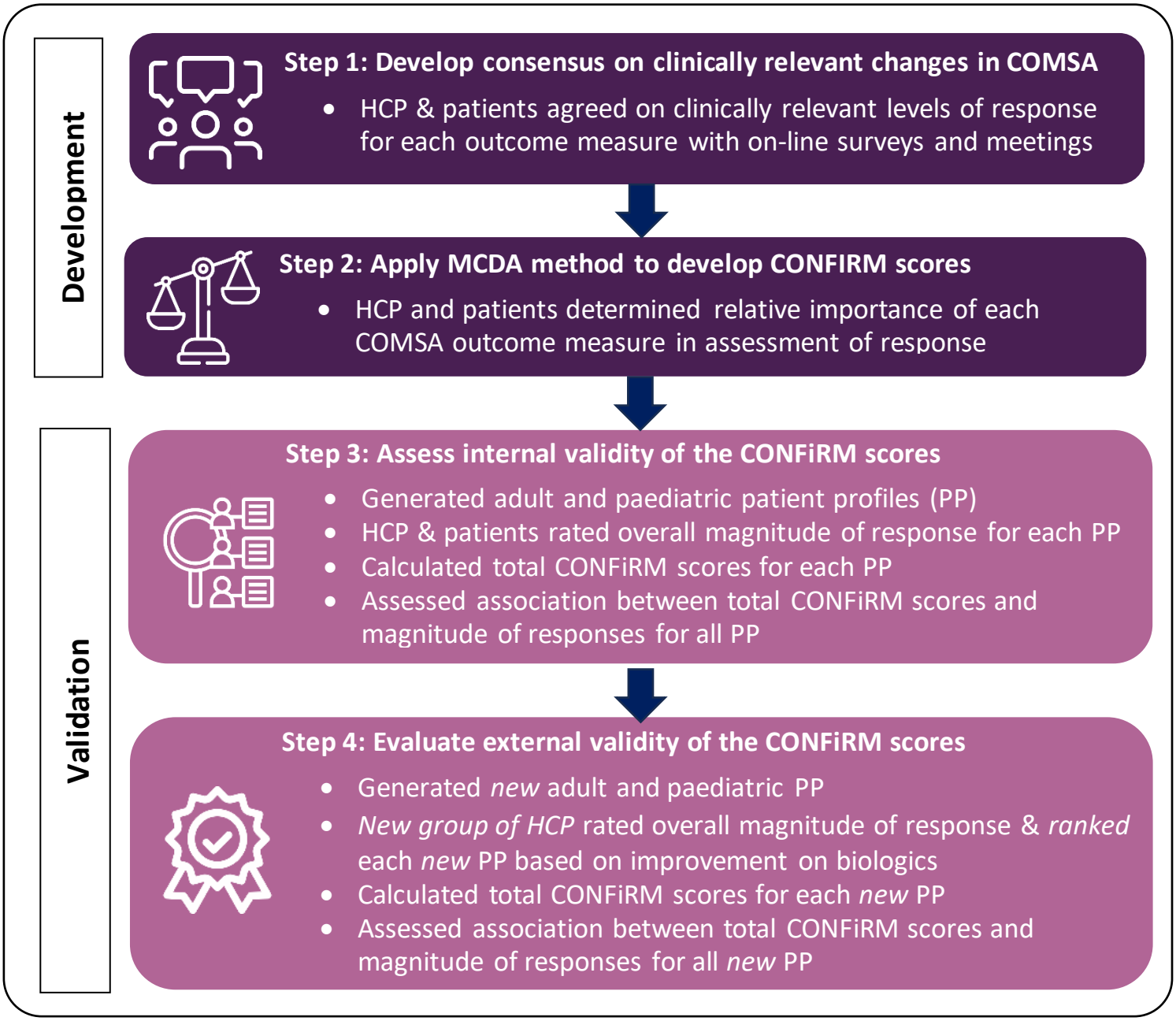


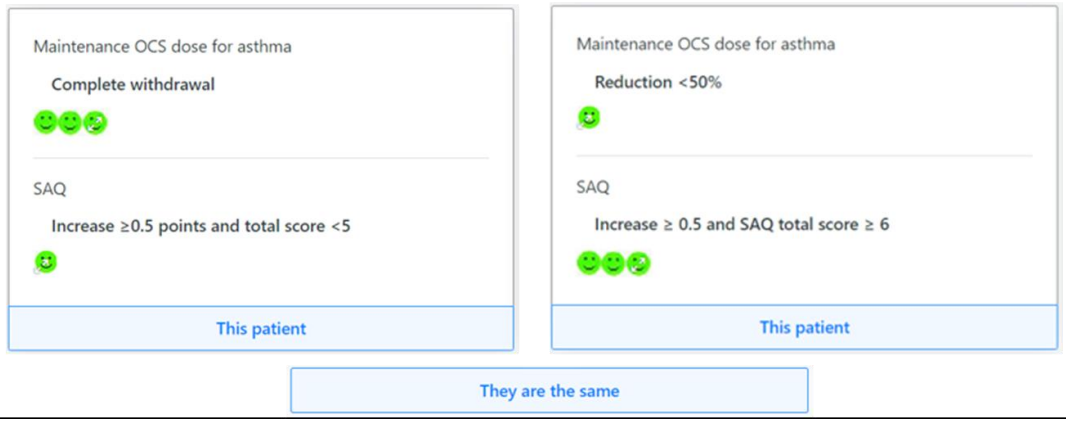
Figure 1

A.

Imagine you are considering two patients with severe asthma who have been treated with a biological and whose patient outcome measures are as shown below.

Which of these two patients' health has improved more?

Assume they are both the same for the other outcome measures



B.

Patient 1: 19 years, male, regular high dose of inhaled corticosteroids, eczema, food allergy, hayfever.

Outcome measures			Data		Change		Changes seen in a patient one year after biological treatment
COMSA		Characteristics	Before	After 1 year therapy	Absolute	Percent	
Asthma control (ACQ-6)	ACQ-5	• Higher score= worse • Range=0-6 points • Score of 1.5 or more indicates poor control	4.8	2.6	↓ 2.2 points	↓ 46%	• Woken by asthma during night – improved from *'A great many times'* to *'A few times'* • Asthma symptoms at night – improved from *'Severe symptoms'* to *'Moderate symptoms'* • Activity limitations – improved from *'Extremely limited'* to *'Slightly limited'* • Shortness of breath – improved from *'A very great deal'* to *'A great deal'* • Wheeze – improved from *'A moderate amount of the time'* to *'Hardly any of the time'*
	Reliever medication use	• Higher score= worse • Range=0-6 points	1	0	↓ 1 point	↓ 100%	• Reliever medication use – improved from *'1 - 2 puffs/inhalations most days'* to *'None'*
Quality of life	SAQ	• Higher score= better • Range=1-7 points	3	3.5	↑ 0.5 points	↑ 15%	• Social, personal & leisure life – improved from *'Difficult'* to *'Moderately difficult'* • Depression, irritable or anxious – no change - *'Difficult'* • Tired, appearance, medicine side effects – improved from *'Difficult'* to *'Moderately difficult'*
	SAQ-global	• Higher=better • Range= 0-100	37	43	↑ 7 points	↑ 18%	• Overall qualify of life – improved from *'Somewhat bad/bad'* to *'Somewhat bad'*
Lung function, (FEV_1, % predicted)		• ≥ 80% =normal	52	57	↑ 5% points	↑ 10%	• Lung function – improved by a very small amount from initially low lung function
Severe asthma attacks, number per year		• None = better	6	2	↓ 4 attacks	↓ 67%	• Severe asthma attacks – improved from 6 attacks a year to 2
Regular oral steroids, prednisolone dose (mg)		• None = better	0	0	No change		• Regular oral steroids for asthma – not treated with them

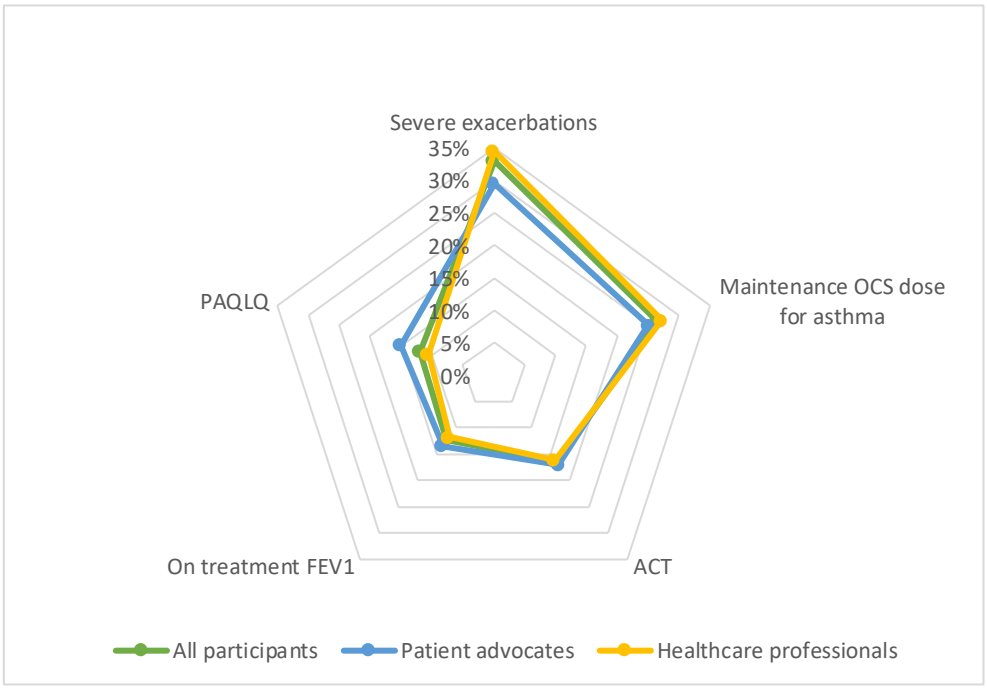
Notes: getting better; no change or negligible change; getting worse.

Has this patient achieved:

☐ Deleterious response ☐ Non-response ☐ Sufficient response ☐ Substantial response ☐ Super-response

Figure 2

A.



B.

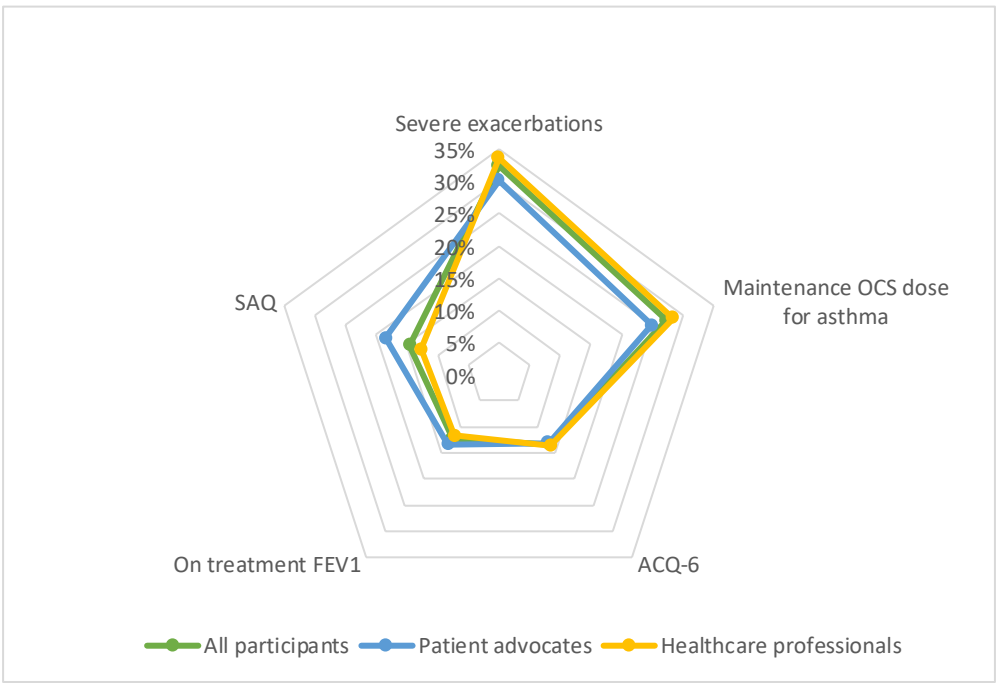
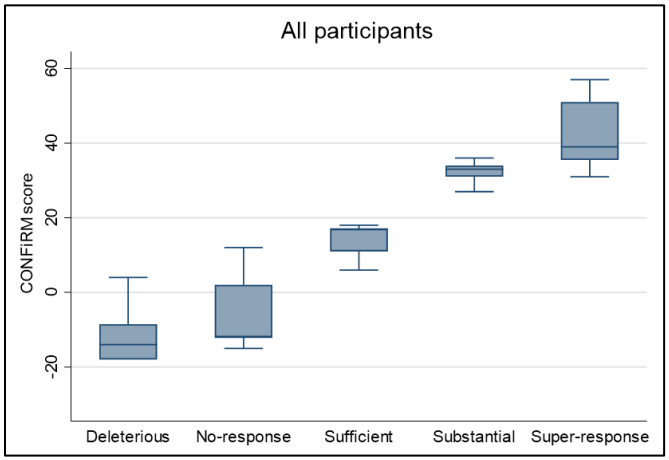
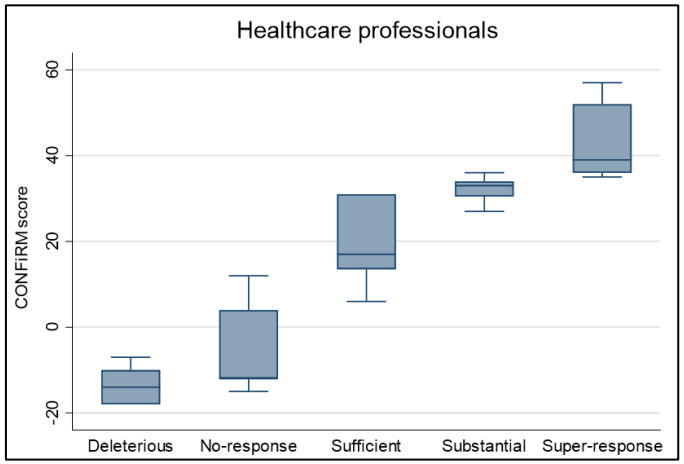
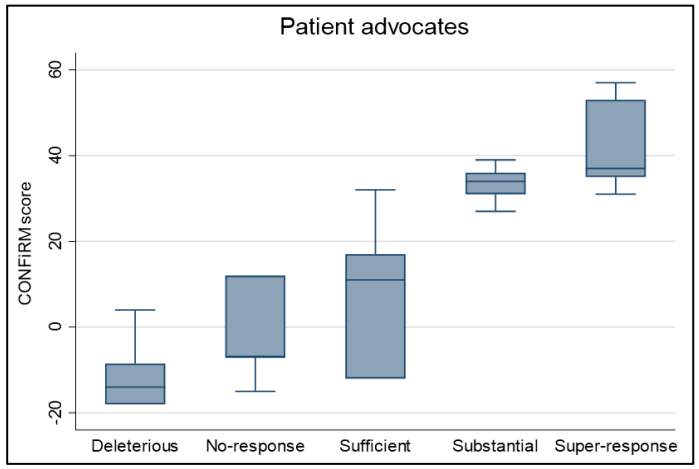


Figure 3

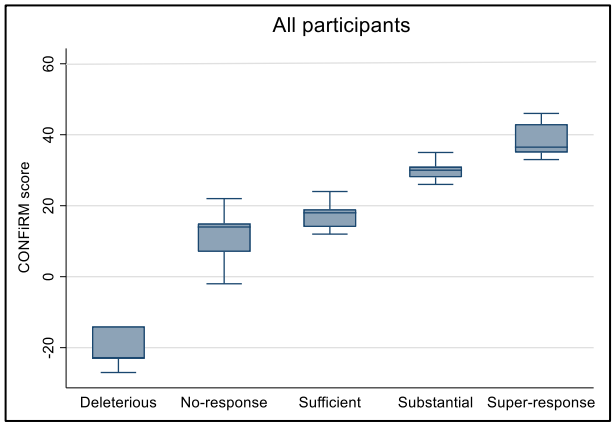
A. Paediatric CONFiRM

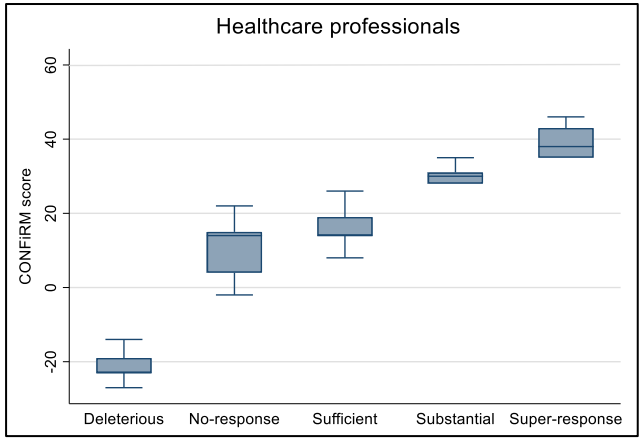






B. Adult CONFiRM





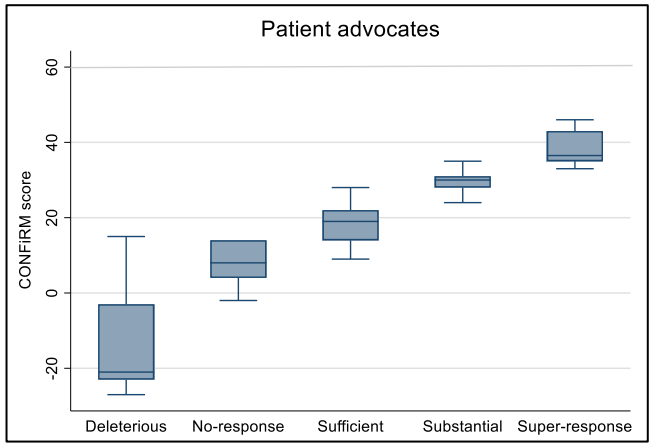
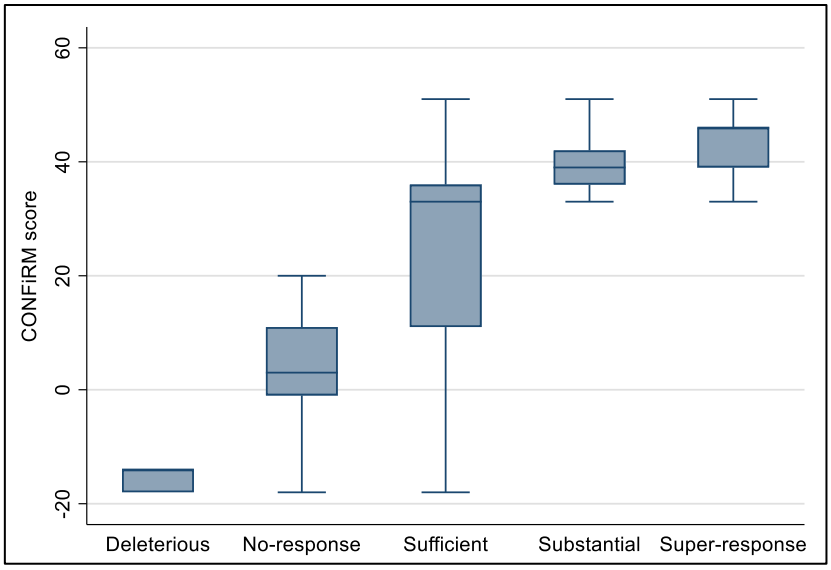


Figure 4

A. Paediatric CONFiRM



B. Adult CONFIRM

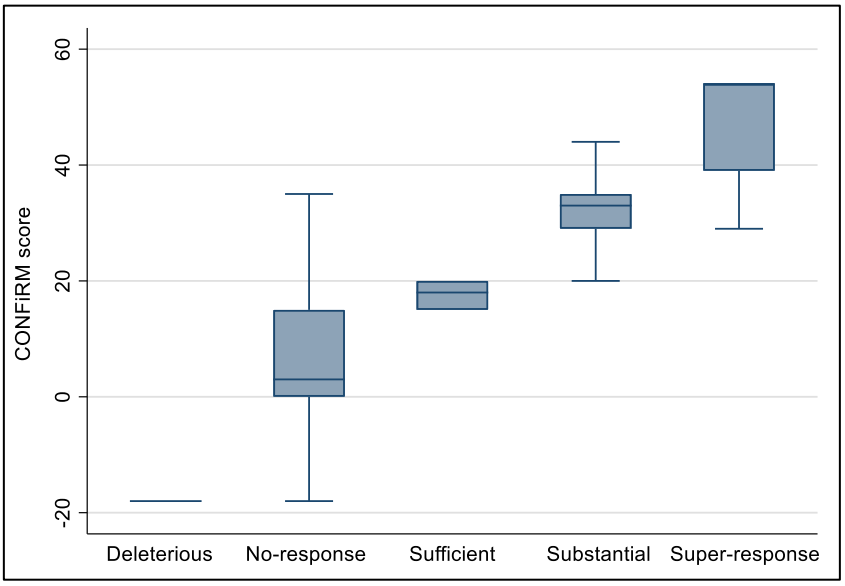
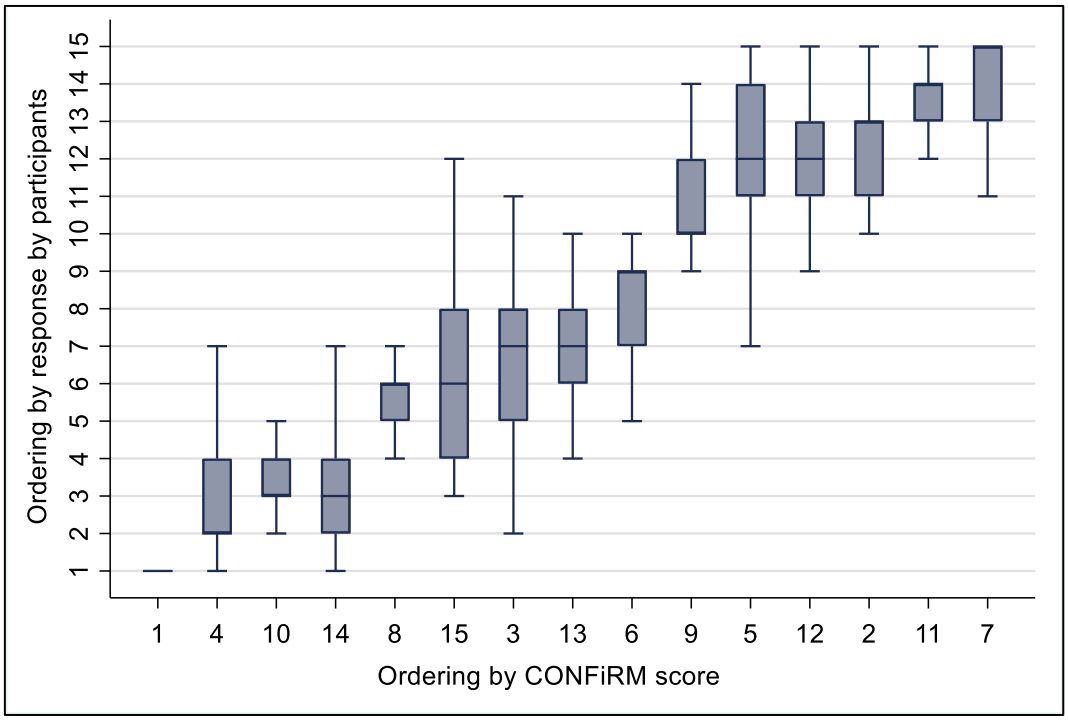


Figure 5

A. Paediatric survey.



B. Adult survey.

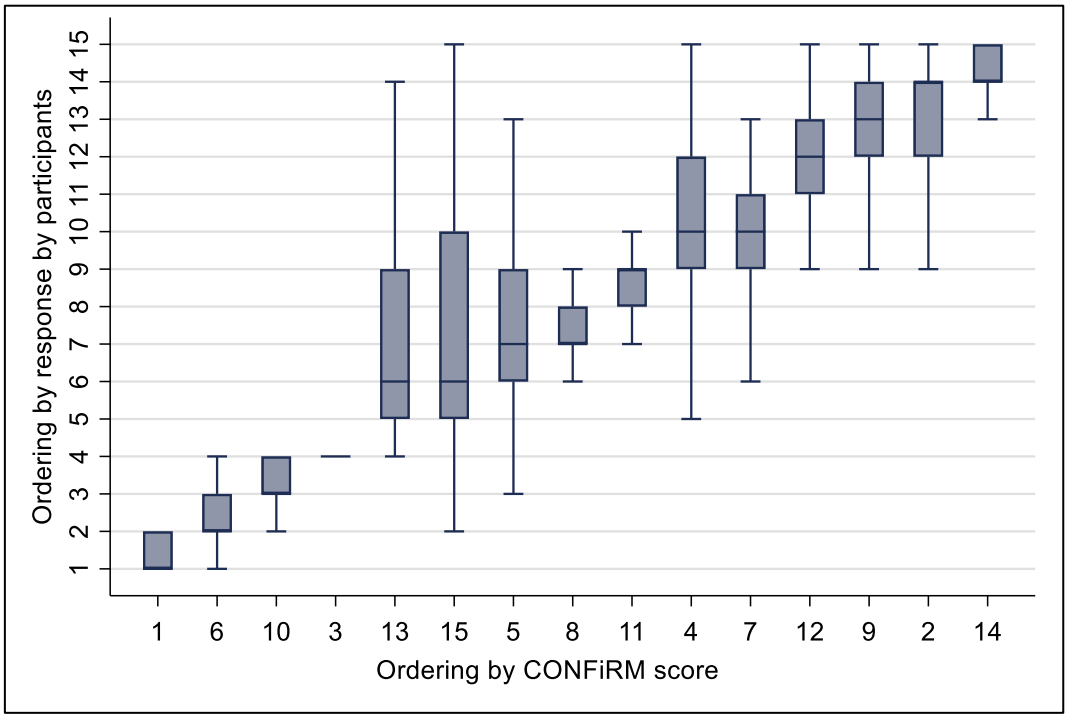


Figure 6

Supplementary materials.

Patient-centred composite scores as tools for assesment of response to biological therapy for paediatric and adult severe asthma.

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Appendix 1. Pilot of study documentation and training of participants

The study documentation was piloted with early career researchers (medical and non-medical) who were not involved in the project to check understanding, time to complete and functionality of the survey questionnaires used to collect the study data. None of the pilot participants found the surveys difficult to understand or burdensome. The surveys were updated according to the feedback and final versions were reviewed by a paediatric psychologist.

Patient advocates and healthcare professionals (HCPs) separately attended training sessions prior to each step to discuss core outcome measures that were selected in the previous part of the 3TR Core Outcome Measures for paediatric and adult Severe Asthma (COMSA) study[1], review a few pilot patient profiles and the survey systems. All participants were required to be able to read and communicate in English. All pre-learning materials were provided before the training sessions, which included information about each step of the study, glossary of terms, characteristics of outcome measures and examples of patient profiles written in lay language. Blank copies of selected questionnaires were also available for participants to review.

Appendix 2. Step 1 methods: Develop consensus levels of clinically relevant changes for each COMSA outcome measure

Initial drafts of levels of response for each paediatric and adult COMSA outcome were developed from the literature in particular minimal clinically importance difference (MCID) and minimal important difference (MID) data. The views of patient advocates and HCPs in the wider consortium were sought with SurveyMonkey® surveys conducted between 29th April and 6th May 2022; 17th and 24th May 2022. The aim of the surveys was to further revise levels of response incorporating views of the two stakeholder groups. Between surveys, there were series of meetings to discuss the results. The consensus was set for at least 80% agreement.

Appendix 3. Step 2 methods: Apply MCDA method to develop CompOsite iNdex For Response in asthMa (CONFiRM)

Multicriteria decision analysis (MCDA) was undertaken using the PAPRIKA (*P*otentially *A*ll *P*airwise *R*an*K*ings of all possible *A*lternatives) method.[2] The PAPRIKA method has been used to develop different questionnaires[3,4] and response criteria[5,6]. We implemented this method using the 1000minds software (1000minds Ltd, New Zealand; www.1000minds.com).

Patient advocates and HCPs received a link to 1000minds website. Each question involved a trade-off between two outcome measures and their levels of response. The pairwise-ranking questions were repeated with different pairs of levels of improvement in each outcome measure. Each time the participant answers a question- all other pairs 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 **(Figure 2a),** if a participant decides that patient response A (complete withdrawal of maintenance OCS dose and increase ≥0.5 SAQ points plus total score <5) is greater than patient response B (reduction from 50% to < 100% in maintenance OCS dose and increase ≥0.5 SAQ points and total score 5 to <6) and then decides patient response B is greater than patient response C (reduction <50% in maintenance OCS dose and increase ≥0.5 point plus SAQ total score ≥6) then by transitivity patient response A is greater than patient response C (and so is not asked by the software). Also, each time a participant answers a question, the PAPRIKA method adapts the selection of pairs of the next question based on all of their preceding answers (always one whose answer was not implied by earlier answers). This adaptivity combined with the above-mentioned elimination procedure based on transitivity ensures that the number of questions asked is minimised while ensuring the participant has pairwise ranked all possible outcome measures with levels defined on two levels of response at a time, either explicitly or implicitly (by transitivity). Final weights were derived based on the linear programming technique.[2]

The consistency of each participant's choices was tested by repeating two previously answered scenarios. Consistent choice was defined as reporting the same response (patient 1 improved most, patient 2 improved most or 'they are the same'). The time that each participant took to answer each scenario was also recorded by the software. Participants who answered their questions implausibly quickly (in less than median 4 seconds per all questions) were excluded from the final analysis.

The relative importance of each COMSA outcome measure in the composites was calculated for each participant and was also averaged across all participants. Median (25% and 75% percentiles) and mean SD weights of each outcome measure were reported for all groups of participants. Box and whisker plots were generated for each overall magnitude of response. Sensitivity analysis was undertaken to compare weighting of each COMSA outcome measure depending on consistency in answering two repeated scenarios and individual expectations of the results. The CONFiRM was developed and re-scaled so non-response had a zero scale. This resulted in a maximal response of 69 and a minimal (deleterious) response of -31.

Patient advocates (12 + years) and paediatric HCPs reviewed paediatric profiles while adult patient advocates (18+ years) and adult HCPs reviewed adult profiles. 'Save and come back' feature was available to allow completion of the survey in multiple attempts. The survey was conducted between 1st and 17th June 2022 with several reminder emails sent to encourage participation.

Appendix 4. Step 3 methods: generating paediatric and adult patient profiles

A study dataset was eligible for inclusion into the study if both criteria were fulfilled 1) patients (>5 years) with doctor-diagnosed severe asthma based on International or European guidelines and 2) prospective data collection from a study with biologic(s) **(Table S1).**

We noted that the response to the biologicals was very heterogenous between patients. As we wanted to select a representative sample, we used a clustering algorithm to separately group paediatric and adult patient profiles with similar responses into clusters. Hierarchical average linkage was used, key variables were the change in each of the COMSA outcome measures. The cut number was set at 50 as we wanted 50 patient profiles (STATA V16.1). One patient was included at random from each group to form the patient profiles. Each patient profile was assigned a frequency weighting on the basis of the total number of patients in its cluster group.

For each patient profile, the following were presented: COMSA before and after 12 months of treatment with a biologic, plus the absolute and relative percentage changes **(Figure 2b).** Each profile also contained information about age, gender, patient's pharmacological therapy and co-morbidities. Participants were

advised to assume that other than mOCS dosage (which formed one of the outcome measures), there were no changes in therapy, adherence nor the patients' environment.

Table S1. Overview of the data used to create patient profiles for the step 3.

Paediatric data (n=581)			Adult data (n=1430)		
Study	**Diagnosis of severe asthma**	**Biological therapy**	**Study**	**Diagnosis of severe asthma**	**Biological therapy**
1. Royal Brompton Hospital,[7] UK (n=78) Real life study	ATS/ERS guideline	Mepolizumab (16) Omalizumab (62)	**1. WATCH study,[8] UK (n = 58)** Real life study	BTS asthma guideline	Mepolizumab (58)
2. PERMEABLE study,[9] Sweden (n=6) Real life study	ATS/ERS guideline	Omalizumab (3) Dupilumab (1) Mepolizumab (2)	**2. The Danish Severe asthma register,[10] Denmark (n=1049)** Real life study	ATS/ERS guideline	Dupilumab (186) Benralizumab (171) Mepolizumab (463) Omalizumab (182) Reslizumab (47)
3. ANCHORS study,[11] Spain (n=484) Real life study	Step 4 or 5 GINA guideline	Omalizumab (484)	**3. SoMOSA study,[12] UK (n=217)** Observational study	Step 4 or 5 GINA guidelines	Omalizumab (217)
4. Birmingham Women's and Children's NHS Foundation Trust, UK (n=13) Real life study	ATS/ERS guideline	Mepolizumab (13)	**4. University Hospitals Plymouth NHS Trust,[13] UK (n=106)** Real-life study	ATS/ERS guideline	Mepolizumab (26) Benralizumab (62) Reslizumab (2) Omalizumab (16)

Table summarises the data used to create patient profiles for the step 3. Once all databases were combined, regression models were used to impute any missing information. Imputations were done for SAQ as we did not have 1 year follow up data (only 6 months) in the University Hospitals Plymouth NHS dataset and ANCHORS study did not collect PAQLQ data. ANCHORS, Asthma iN CHildren: Omalizumab in Real-life in Spain; ATS, American Thoracic Society; BTS, British Thoracic Society; ERS, European Respiratory Society; GINA, Global Initiative for Asthma; NHS, National Health Service; PERMEABLE, PERsonalized MEdicine Approach for asthma and allergy Biologicals seLEction; SOMOSA, Study of Mechanisms of Action of Omalizumab in Severe Asthma; WATCH study, The Wessex AsThma CoHort; UK, United Kingdom.

Appendix 5. Step 3 methods: Overview of the stakeholder survey to select definitions of response

As part of the development of the project, a survey was conducted between 3rd and 13th November 2020. The aim was to decide on the working terminology of non-response and response as well as to better understand any differences of opinions between stakeholder groups. We received 52 responses from 29 (55.8%) experienced clinicians, 17 (32.7%) patient advocates, 5 (9.6%) regulators and 1 (1.9%) pharmaceutical representative. All were from the 3TR respiratory working group which has members from across Europe.[1] The following overall magnitudes of response were agreed by at least 80% of the stakeholders: deleterious/negative response, non-response, minimal clinically important difference (MCID)/sufficient response, substantial response and super-response. Their definitions are reported in **Box 1.**

Appendix 6. Step 3 methods: Rating of overall magnitude of response for each patient profile

The consistency of each participant's ratings was assessed by repeating two patient profiles. A consistent choice was defined as reporting the same magnitude of response. A free-text box was available for comments at the end of the survey. Patient advocates (12+ years) and paediatric HCPs reviewed paediatric profiles while adult patient advocates (18+ years) and adult HCPs reviewed adult profiles. The 'save and come back' feature was available to allow completion of the survey in multiple attempts. The survey was conducted between 4th March and 20th March 2022 with two reminder emails sent to encourage participation.

Classification of response based on five overall magnitude of response was reported in percentages for patient advocates and HCPs. Intraclass correlation coefficient[14] (ICC) estimates were used to calculate agreement between responses for the repeated patient profiles from all participants, patient advocates and HCPs. ICC and their 95% confident intervals were calculated based on an absolute-agreement, 2-way mixed-effects model. Values less than 0.5 are indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.90 indicate excellent reliability. Kruskal-Wallis test was used to assess differences between each magnitude of response definition.

For initial validation of the two CONFiRMs, a receiver operating characteristic (ROC) and the area under the curve (AUC) with 95% confidence intervals (CI) was computed for sufficient and substantial definitions of response. We compared the CONFiRM score with the FEOS (FEV_1, exacerbations, OCS, symptoms)[5] definitions of response using Pearson correlation. Additionally, we compared the CONFiRM score with the super-response definition[15] using a ROC and AUC analysis. Where necessary, levels were harmonized to allow comparison. Sensitivity analysis was performed for patient profiles who were taking or not taking

maintenance oral corticosteroids (mOCS) at baseline. A bootstrapping approach was additionally undertaken to minimise overfitting. In this approach, resampling with replacement was used with 1000 replications.

Appendix 7. Step 4 methods: Assess external validity of the CONFiRM scores

Additional 15 adult and 15 paediatric patient profiles were generated from the same dataset **(Table S1).** A new case was identified from each cluster. 15 patient profiles were selected to provide an equal number of profiles for each of the 5 overall magnitudes of response. Total CONFiRM score was calculated for each patient profile. A separate group of HCPs was recruited using similar approach as in the step 1-3. They rated each patient profile in terms of 5 overall magnitudes of response in the Qualtrics software. Additionally, they ordered patient profiles based on improvement on a biologic. Association between the total CONFiRM score (step 2) and the magnitude of response (step 4) for these patient profiles was assessed using Spearman correlation.

The same analysis as in stage 3 was done. Additionally, agreements between ranking of patient profiles and CONFIRM's total scores were assessed using Spearman correlation. Four and six participants from adult and paediatric surveys were removed from the analysis as they ranked patient profiles in the opposite way (from the largest to smallest improvement).

Appendix 8. Statistical considerations

Continuous variables are described by mean and standard deviation or median and interquartile range. Categorical variables are described by counts and proportions as percentages.

The study sample size for step 1-3 was calculated based on precision in estimating change in the response score for each of the five response definitions. It was planned to have at least 30 participants in each stakeholder group (HCPs and patient advocates) with each rating 50 patient profiles in the step 3. We assumed an equal number of patient profiles for each of the five potential response definitions. Therefore, we planned to have 30 ratings of 10 patient profiles for each overall magnitude of response definition. As an example of power, if the estimated mean change for a response definition is 10 (on a 100-point scale) and the associated standard deviation is 2, the 95% confidence interval for the estimate would be 9.7 to 10.2; for a larger standard deviation of 4, the 95% confidence interval for the estimate would be 9.5 to 10.5 (STATA v16.1).

The sample size for step 4 (35 adult and 35 paediatric clinicians) was based on achieving a representative group of clinicians from multiple countries.

Appendix 9. Step 1 results: Develop consensus levels of clinically relevant changes for each COMSA outcome measure

Table S2. Demographic information of the stakeholder survey participants to select levels of response

Stakeholders	Survey 1		Survey 2	
	Paediatric n (%)	Adult n (%)	Paediatric n (%)	Adult n (%)
Patients with severe asthma (<18 years)	4 (6.6)	0 (0.0)	3 (4.2)	0 (0.0)
Patients with severe asthma (> 18 years)	16 (26.2)	18 (32.7)	25 (34.7)	25 (36.2)
Caregivers of children with severe asthma	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)
Patient representatives	2 (3.3)	2 (3.6)	4 (5.6)	4 (5.8)
Healthcare professionals	37 (60.6)	35 (63.7)	40 (55.6)	40 (58.0)
Total	**61 (100.0)**	**55 (100.0)**	**72 (100.0)**	**69 (100.0)**

Figures represent number (percentage) of participants.

Table S3. Final agreements for levels of clinically relevant changes in paediatric and adult COMSA

Paediatric COMSA	Total n (%)	PA n (%)	HCP n (%)	Adult COMSA	Total n (%)	PA n (%)	HCP n (%)
Severe asthma attacks[5]: change relative to previous 12 months				**Severe asthma attacks[5]:** change relative to previous 12 months			
Increase[#]	55 (91.7)	22 (95.7)	33 (89.2)	Increase[#]	53 (98.1)	18 (94.7)	35 (100.0)
No change[##]				No change[##]			
Reduction <50%				Reduction <50%			
Reduction from 50% to < 100%				Reduction from 50% to < 100%			
100% reduction				100% reduction			
Maintenance OCS dose for asthma:[5] change relative to baseline				**Maintenance OCS dose for asthma:[5]** change relative to baseline			
Increase*	61 (100.0)	24 (100.0)	37 (100.0)	Increase*	53 (96.4)	18 (90.0)	35 (100.0)
No change**				No change**			
Reduction <50%				Reduction <50%			
Reduction from 50% to < 100%				Reduction from 50% to < 100%			
Complete withdrawal***				Complete withdrawal***			
On treatment FEV_1[◊]: change relative to the predicted FEV_1 value at baseline				**On treatment FEV_1[◊]:** change relative to the predicted FEV_1 value at baseline			
Decrease ≥10%[16]	65 (90.3)	31 (96.9)	34 (85.0)	Decrease ≥10%[16]	64 (92.8)	28 (96.6)	36 (90.0)
No change (decrease <10% or increase <10%)				No change (decrease <10% or increase <10%)			
Increase from 10% to <15%				Increase from 10% to <15%			
Increase from 15% to <20%				Increase from 15% to <20%			
Increase ≥20%				Increase ≥20%			
ACT questionnaire: change relative to baseline				**ACQ-5 questionnaire:** change relative to baseline			
Decrease ≥ 2 points[17]	63 (88.7)	30 (96.8)	33 (82.5)	Increase ≥0.5 points[18]	64 (92.8)	27 (93.1)	37 (92.5)
No change (increase <2 or decrease <2 points)				No change (increase <0.5 or decrease <0.5 points)			
Increase ≥2 points and total score ≤19[19]				Decrease ≥0.5 points and total score >1.5[20]			
Increase ≥2 points and total score 20 to <23[17]				Decrease ≥0.5 points and total score from >0.75 to 1.5			
Increase ≥ 2 points and total score ≥ 23				Decrease ≥0.5 points and total score ≤0.75[20]			
C-ACT questionnaire: change relative to baseline							
Decrease ≥ 2 points[17]	62 (88.6)	28 (93.3)	34 (85.0)				
No change (increase <2 or decrease < 2 points)							
Increase ≥2 points and total score ≤19[19]							
Increase ≥2 points and total score 20 to <22[17]							
Increase ≥ 2 points and total score ≥ 22							

Paediatric COMSA				Adult COMSA			
	Total n (%)	PA n (%)	HCP n (%)		Total n (%)	PA n (%)	HCP n (%)
PAQLQ questionnaire: change relative to baseline				**SAQ questionnaire:** change relative to baseline			
Decrease ≥ 0.5 points[21]	63 (90.0)	26 (86.7)	37 (92.5)	Decrease ≥ 0.5 points[22]	67 (97.1)	27 (93.1)	40 (100.0)
No change (increase <0.5 or decrease <0.5 points)				No change (increase <0.5 or decrease <0.5 points)			
Increase ≥ 0.5 points and total score < 5				Increase ≥0.5 points and total score <5			
Increase ≥ 0.5 points and total score 5 to < 6				Increase ≥0.5 points and total score 5 to <6			
Increase ≥ 0.5 points and total score ≥ 6				Increase ≥0.5 points and total score ≥6			

Figures represent number (%) of participants agreeing with final levels of response of paediatric and adult COMSA. For each outcome, there are five levels of change are presented: worsening, no change, small change, moderate change and large change.

Severe asthma attacks are defined as per ERS/ATS guideline.[23] Maintenance oral corticosteroid use is defined as daily or alternate day use of oral corticosteroids. C-ACT is for children 6-11 years and ACT is for children from 12-18 years.

*Or if the patient was not receiving maintenance oral corticosteroids and started the drug. **Or if the patient was not receiving maintenance oral corticosteroids and remained without them. ***Low dose of maintenance oral corticosteroid for adrenal insufficiency should be treated as withdrawal of maintenance oral corticosteroid.[5]

[#]Or if the patient was free of severe asthma attacks. [##]Or if the patient was free of asthma attacks and continued to have no severe asthma attacks.[5]

[◊] Change in on treatment FEV_1 is calculated as [(follow up FEV_1 minus baseline FEV_1 divided by predicted FEV_1 value) x 100][16]. This is on treatment measurement meaning that a patient may have recently had a LABA but will not have had a large dose of a SABA as per a post-bronchodilator FEV1. Changes over time have been demonstrated to be dependent on age, sex, baseline lung function and disease severity, limiting the generalisability of these approaches. It is recommended that an abnormal lung function is defined as a z score below -1.645. In this project % predicted is being used only because it was felt to be more comprehensible for patients participating in the project.

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Test; COMSA, Core Outcome Measures sets for paediatric and adult severe asthma; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroids; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; PA. patient advocates; HCP, healthcare professionals; SAQ, Severe Asthma Questionnaire.

Appendix 10. Step 2 results: Apply MCDA method to develop CONFiRMs scores

The same group of participants as step 1 took part including 63 [42 (66.7.0%) HCPs; 21 (33.3%) patient advocates] and 66 [46 (69.7%) HCPs; 20 (30.3%) patient advocates] for the adult and paediatric parts respectively. Demographic characteristics are shown in **Table S4.**

All participant groups assigned the highest relative importance to severe asthma exacerbations and mOCS in both adult and paediatric CONFiRMs (**Figure S1**). Patient advocates and HCP weighted each COMSA outcome equally as show by their ranking in **Figure 3.** The exception was that patient advocates rated asthma-specific QoL higher than HCPs (**Figure 3**). **Table S5** shows median and mean ratings for each COMSA outcome for patient advocates and HCPs. Weights of outcome measures in the CONFiRM from 1000Mind software by patient advocates and healthcare professionals are shown in **Table S6**.

Most participants gave the same answer for two repeated patient profiles (54 (81.8%) and 49 (77.8%) participants for paediatric and adult, respectively)(**Table S7**). Most participants took more than 12 seconds to decide on each answer (**Figure S2**). Weights were also similar in the sensitivity analysis focused on participants who answered the repeated scenarios consistently (**Tables S7, S8, S9**). Most participants also felt the order of the COMSA outcomes in terms of importance was rights (**Tables S10, S11**).

Table S4. Overall demographic information about survey respondents in step 2

A. All participants

	Adult profiles n (%)		Paediatric profiles n (%)	
	Healthcare professionals n=42	Patient advocates n=21	Healthcare professionals n=46	Patient advocates n=20
Country				
United Kingdom	12 (28.6)	8 (38.1)	14 (30.4)	7 (35.0)
Sweden	3 (7.1)	4 (19.0)	2 (4.3)	4 (20.0)
Germany	5 (11.9)	0 (0.0)	4 (8.7)	0 (0.0)
Netherlands	2 (4.8)	2 (9.5)	4 (8.7)	1 (5.0)
Canada	3 (7.1)	1 (4.8)	1 (2.2)	1 (5.0)
France	2 (4.8)	0 (0.0)	3 (6.5)	1 (5.0)
Belgium	1 (2.4)	2 (9.5)	0 (0.0)	2 (10.0)
Italy	0 (0.0)	1 (4.8)	2 (4.3)	2 (10.0)
Australia	3 (7.1)	0 (0.0)	1 (2.2)	0 (0.0)
Others*	11 (26.2)	3 (14.3)	15 (32.6)	2 (10.0)
Gender				
Male	25 (59.5)	4 (19.0)	20 (43.5)	4 (20.0)
Female	17 (40.5)	17 (81.0)	26 (56.5)	15 (75.0)
Prefer not to say	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)
Age group, years				
12-17	0 (0.0)	0 (0.0)	0 (0.0)	3 (15.0)

18-25	0 (0.0)	2 (9.5)	0 (0.0)	3 (15.0)
26-36	4 (9.5)	2 (9.5)	1 (26.1)	3 (15.0)
37-47	7 (16.7)	4 (19.0)	12 (26.1)	6 (30.0)
48-58	19 (45.2)	9 (42.9)	19 (41.3)	2 (10.0)
59-69	9 (21.4)	3 (14.3)	13 (28.3)	2 (10.0)
70-80	3 (7.1)	1 (4.8)	1 (2.2)	1 (5.0)

B. Demographic information about patient advocates

Patients n (%)	**Adult profiles n (%) n=19**	**Paediatric profiles n (%) n=18**
During the last year I had		
two or more courses of steroid tablets such as prednisone to treat asthma attacks	8 (42.1)	6 (33.3)
treatment daily or every other day with steroid tablets such as prednisone	5 (26.3)	7 (38.9)
an emergency hospital admission or ED admission due to asthma	4 (21.1)	6 (33.3)
none of the above	9 (47.4)	8 (44.4)
don't know	0 (0.0)	1 (5.6)
Previously taken/are currently taking biological therapy for asthma		
Yes, previously taken biological therapy	3 (15.8)	3 (16.7)
Yes, currently taking biological therapy	12 (63.2)	12 (66.7)
No	4 (21.1)	3 (16.7)
Switched from one biological therapy for asthma to another biological therapy		
Yes	5 (26.3)	5 (27.8)
Duration of severe asthma		
Median (25^{th};75^{th} percentile), years	25 (12.0; 42.0)	14.0 (10.1-26.3)
Other allergic conditions**		
Food allergy	11 (57.9)	11 (61.1)
Urticaria	8 (42.1)	6 (33.3)
Allergic rhinitis and/or conjunctivitis	15 (78.9)	14 (77.8)
Atopic dermatitis or eczema	8 (42.1)	5 (27.8)
Anaphylaxis in the past	5 (26.3)	7 (38.9)
Allergy to stings from wasps or bees	3 (15.8)	2 (11.1)
Allergic reaction to a medicine	9 (47.4)	7 (38.9)
None of the above	2 (10.5)	2 (11.1)
Patient organisation representatives n (%)	**Adult profiles n (%) n=2**	**Paediatric profiles n (%) n=2**
Duration of being a patient representative in the severe asthma field:		
0-2 years	1 (50.0)	1 (50.0)
6-10 years	1 (50.0)	1 (50.0)

C. Demographic information about healthcare professionals

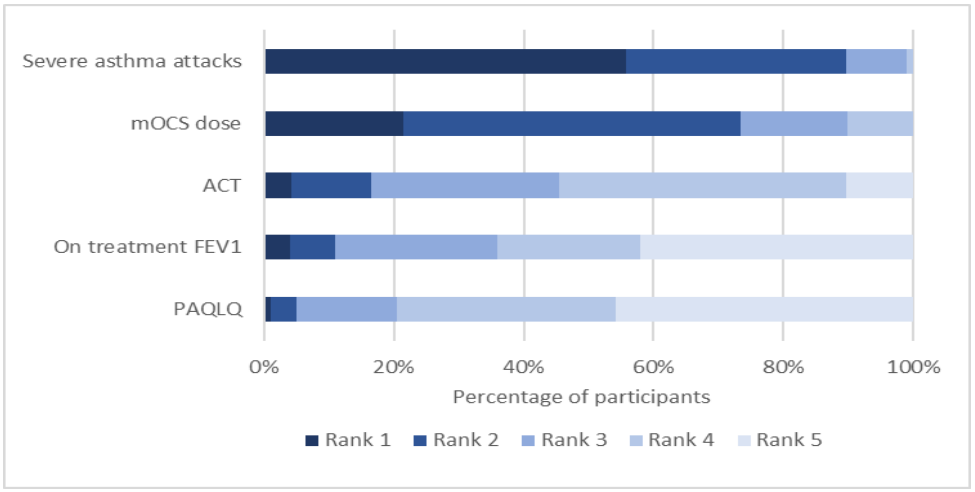
	Adult profiles n (%) n=42	**Paediatric profiles n (%) n=46**
Duration of treating patients with severe asthma		
0-5 years	1 (2.4)	3 (6.5)
5-10 years	5 (11.9)	2 (4.3)
10-20 years	16 (38.1)	18 (39.1)
Over 20 years	20 (47.6)	23 (50.0)

Part of an advisory board, national/international severe asthma working group in the past 5 years		
Yes	32 (76.2)	30 (65.2)
No	10 (23.8)	16 (34.8)
Author of a severe asthma and biological therapies publication in the past 5 years		
Yes	33 (78.6)	38 (82.6)
No	9 (21.4)	8 (17.4)
Practice setting		
Academic hospital/clinic	38 (90.5)	45 (97.8)
Non-academic hospital/clinic	4 (9.5)	1 (2.2)
Work in a specialist severe asthma unit		
Yes	35 (83.3)	41 (89.1)
No	6 (14.3)	4 (8.7)
Not applicable	1 (2.4)	1 (2.2)
Number of patients with severe asthma on biological therapy per year under your care		
<5	0 (0.0)	3 (6.5)
5-10	2 (4.8)	13 (28.3)
11-20	7 (16.7)	17 (37.0)
21-50	12 (28.6)	8 (17.4)
51-100	5 (11.9)	1 (2.2)
101-200	4 (9.5)	2 (4.3)
>201	12 (28.6)	2 (4.3)
Speciality**		
Allergist	14 (33.3)	13 (28.3)
Pneumologist/ pulmonologist/ respiratory physician	30 (71.4)	19 (41.3)
Paediatrician	3 (7.1)	33 (71.7)
Asthma/Respiratory nurse	2 (4.8)	2 (4.3)
Clinical researcher	6 (14.3)	6 (13.0)
Pharmacist	1 (2.4)	0 (0.0)
Dermatologist	1 (2.4)	0 (0.0)
Internal medicine physician	1 (2.4)	0 (0.0)
Dermatologist	0 (0.0)	1 (2.2)
Looking after		
Adults with severe asthma only (≥ 18 years)	32 (76.2)	2 (4.3)
Paediatric patients with severe asthma only (6-17years)	0 (0.0)	34 (73.9)
Both adult and paediatric patients with severe asthma	10 (23.8)	10 (21.7)

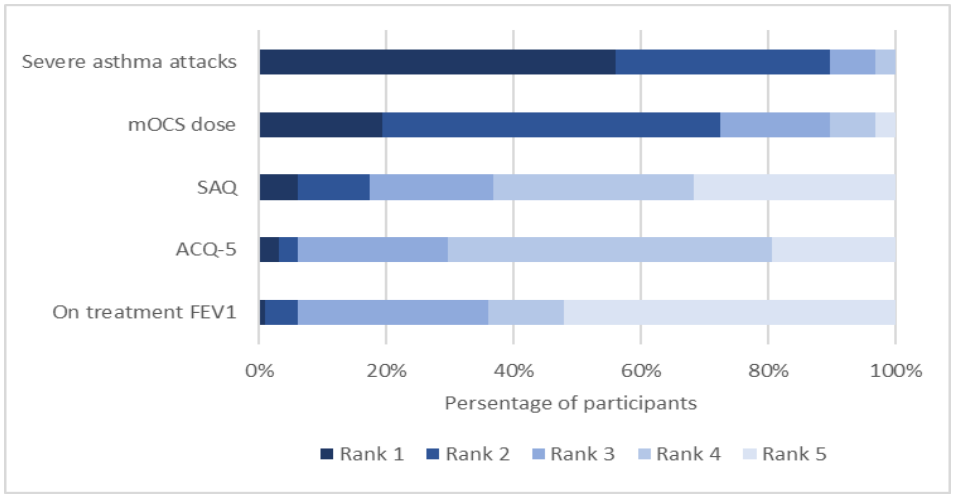
Figures represent number (percentage) of participants.* Others: Czech Republic (n=3); Finland (n=3); Poland (n=3); Spain (n=3); Switzerland (n=3); United States (n=3); China (n=2); Denmark (n=2); Turkey (n=2); Estonia (n=1); Greece (n=1); Japan (n=1); Norway (n=1); Romania (n=1); Singapore (n=1); Slovenia (n=1). ** all answers that are applicable. Numbers represent count (percentage) unless otherwise indicated.

Figure S1. Distribution of outcome measure rankings in the CONFiRM (step 2)

A. Paediatric CONFiRM



B. Adult CONFiRM



Bars show percentages of participants who ranked each COMSA outcome measure from 1st (most important) to 5th (less important) in the CONFiRM to biologics. Severe asthma attacks are defined as per ATS/ERS guideline.[23] Maintenance oral corticosteroid use is defined as daily or alternate day use of oral corticosteroids. ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; CONFiRM, CompOsite iNdex For Response in asthMa; FEV_1, percent predicted forced expiratory volume in 1 second; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; OCS, oral corticosteroids; SAQ, Severe Asthma Questionnaire.

Table S5. Outcome measure rankings by all survey participants (step 2)

A. Paediatric CONFiRM

	All participants (n=66)		HCPs (n=46)		Patient advocates (n=20)	
	Median (25th-75th percentile)	Mean (SD)	Median (25^{th}-75^{th} percentile)	Mean (SD)	Median (25^{th}-75^{th} percentile)	Mean (SD)
Severe asthma attacks	1.0 (1.0-2.0)	1.5 (0.8)	1.0 (1.0-1.6)	1.5 (0.7)	1.3 (1.0-2.0)	1.8 (1.0)
Maintenance OCS dose for asthma	2.0 (1.5-2.6)	2.1 (0.9)	2.0 (1.5-2.0)	2.0 (0.7)	2.0 (1.0-3.4)	2.3 (1.2)
ACT questionnaire	3.5 (3.0-4.0)	3.4 (1.0)	3.5 (3.0-4.0)	3.4 (1.0)	3.5 (3.0-4.0)	3.3 (0.9)
On treatment FEV_1	4.0 (3.0-5.0)	3.9 (1.1)	4.0 (3.0-5.0)	3.9 (1.1)	4.0 (3.0-5.0)	3.9 (1.2)
PAQLQ questionnaire	4.0 (4.0-5.0)	4.1 (1.0)	4.0 (4.0-5.0)	4.3 (0.8)	4.0 (2.6-5.0)	3.8 (1.3)

B. Adult CONFiRM

	All participants (n=63)		HCPs (n=42)		Patient advocates (n=21)	
	Median (25^{th}-75^{th} percentile)	Mean (SD)	Median (25^{th}-75^{th} percentile)	Mean (SD)	Median (25^{th}-75^{th} percentile)	Mean (SD)
Severe asthma attacks	1.0 (1.0-2.0)	1.5 (0.7)	1 (1.0-2.0)	1.5 (0.7)	1.0 (1.0-2.0)	1.6 (0.8)
Maintenance OCS dose for asthma	2.0 (1.5-2.5)	2.1 (0.9)	2 (1.5-2.0)	1.9 (0.6)	2.5 (1.8-3.3)	2.6 (1.2)
SAQ questionnaire	4.0 (3.0-5.0)	3.6 (1.2)	4. (3.4-5)	3.9 (1.1)	3.0 (2.0-4.5)	3.1 (1.3)
ACQ-5 questionnaire	4.0 (3.0-4.0)	3.7 (0.9)	4 (3.0-4.0)	3.7 (0.8)	4.0 (3.0-4.0)	3.7 (1.1)
On treatment FEV_1	4.5 (3.0-5.0)	4.1 (1.1)	4.8 (3.0-5.0)	4.1 (1.0)	4.5 (3.0-5.0)	4.0 (1.2)

Tables show each participant's ranking from 1^{st} to 5^{th} for the outcome measures with respect to their relative importance or weight. Severe asthma attacks are defined as per ATS/ERS guideline.[23] Maintenance oral corticosteroid use is defined as daily or alternate day use of oral corticosteroids. ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; CONFiRM, CompOsite iNdex For Response in asthMa; FEV1, forced expiratory volume in 1 second; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; OCS, oral corticosteroids; HCP, healthcare professionals; SAQ, Severe Asthma Questionnaire.

Table S6. Weights of outcome measures in the CONFiRM from 1000Mind software by patient advocates and healthcare professionals (step 2)

A. Paediatric CONFiRM

	Mean weights, %		
	Total (n=66)	**Patient advocates (n=20)**	**Healthcare professionals (n=46)**
Severe asthma attacks[5,24]: change relative to previous 12 months			
Increase[#]	0.0	0.0	0.0
No change[##]	10.5	9.6	10.9
Reduction <50%	19.7	17.9	20.5
Reduction from 50% to < 100%	27.0	24.3	28.1
100% reduction	33.0	29.5	34.5
Maintenance OCS dose for asthma:[5] change relative to baseline			
Increase*	0.0	0.0	0.0
No change**	8.1	7.8	8.3
Reduction <50%	15.4	14.7	15.7
Reduction from 50% to < 100%	21.3	20.2	21.8
Complete withdrawal***	26.5	25.0	27.2
ACT questionnaire[&]: change relative to baseline			
Decrease ≥ 2 points[17]	0.0	0.0	0.0
No change (increase <2 or decrease < 2 points)	4.8	5.1	4.6
Increase ≥2 points and total score ≤19[19]	9.1	9.8	8.9
Increase ≥2 points and total score 20 to <23[17]	12.9	13.6	12.6
Increase ≥ 2 points and total score ≥ 23	16.4	17.0	16.1
On treatment FEV_1[◊]: change relative to the predicted FEV_1 value at baseline			
Decrease ≥10%[16]	0.0	0.0	0.0
No change (decrease <10% or increase <10%)	4.4	5.2	4.1
Increase from 10% to <15%	7.9	9.1	7.4
Increase from 15% to <20%	10.3	11.6	9.8
Increase ≥20%	12.2	13.4	11.7
PAQLQ questionnaire^: change relative to baseline			
Decrease ≥ 0.5 points[21]	0.0	0.0	0.0
No change (increase < 0.5 or decrease < 0.5 points)	3.0	3.7	2.7
Increase ≥ 0.5 points and total score < 5	6.0	7.5	5.4
Increase ≥ 0.5 points and total score 5 to < 6	9.0	11.3	8.0
Increase ≥ 0.5 points and total score ≥ 6	11.9	15.0	10.5

B. Adult CONFiRM

	Mean weights, %		
	Total (n=63)	**Patient advocates (n=21)**	**Healthcare professionals (n=42)**
Severe asthma attacks:[5,24] change relative to previous 12 months			
Increase[#]	0.0	0.0	0.0
No change[##]	10.1	9.0	10.6
Reduction <50%	19.0	17.2	19.9
Reduction from 50% to < 100%	26.3	24.1	27.3
100% reduction	32.4	30.1	33.6
Maintenance OCS dose for asthma:[5] change relative to baseline			
Increase*	0.0	0.0	0.0
No change**	8.6	7.6	9.1
Reduction <50%	16.1	14.4	16.9
Reduction from 50% to < 100%	22.1	20.0	23.1
Complete withdrawal***	27.3	24.9	28.4
SAQ questionnaire[&]: change relative to baseline			
Decrease ≥ 0.5 points[22]	0.0	0.0	0.0
No change (increase <0.5 or decrease <0.5 points)	4.3	4.7	4.1
Increase ≥0.5 points and total score <5	8.1	9.2	7.6
Increase ≥0.5 points and total score 5 to <6	11.5	13.8	10.4
Increase ≥0.5 points and total score ≥6	14.6	18.5	12.7
ACQ-5 questionnaire[^]: change relative to baseline			
Increase ≥0.5 points[18]	0.0	0.0	0.0
No change (increase <0.5 or decrease <0.5 points)	3.6	2.9	4.0
Decrease ≥0.5 points and total score >1.5[20]	7.1	6.0	7.7
Decrease ≥0.5 points and total score from >0.75 to 1.5	10.3	9.4	10.8
Decrease ≥0.5 points and total score ≤0.75[20]	13.4	13.0	13.6
On treatment FEV_1[◊]: change relative to the predicted FEV_1 value at baseline			
Decrease ≥10%[16]	0.0	0.0	0.0
No change (decrease <10% or increase <10%)	4.3	4.6	4.2
Increase from 10% to <15%	7.8	8.3	7.6
Increase from 15% to <20%	10.3	11.1	10.0
Increase ≥20%	12.3	13.4	11.7

Figures represent weights (as points) for each COMSA outcome by level. These weights were generated by the 1000minds software and used to generate the composite score with an adjustment made to centre non-response on zero. These weights are raw data from 1000minds before the score was re-scaled so that 0 represented no change. ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; CONFiRM, CompOsite iNdex For Response in asthMa; FEV_1, forced expiratory volume in 1 second; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; OCS, oral corticosteroids; SAQ, Severe Asthma Questionnaire. Please see further footnotes in **Table S3.**

Table S7. Weights of outcome measures from 1000Mind software in the composite assigned by all participants and those who consistently answered two repeated scenarios (step 2)

A. Paediatric CONFiRM

	All participants (n=66)		Participants answered 2 scenarios consistently (n=54)	
	Mean weights, %	SD	Mean weights, %	SD
Severe asthma attacks[5,24]: change relative to previous 12 months				
Increase[#]	0.0	0.0	0.0	0.0
No change[##]	10.5	3.5	10.3	3.5
Reduction <50%	19.7	6.0	19.4	6.0
Reduction from 50% to < 100%	27.0	7.4	26.5	7.4
100% reduction	33.0	8.9	32.4	8.9
Maintenance OCS dose for asthma[5]: change relative to baseline				
Increase*	0.0	0.0	0.0	0.0
No change**	8.1	2.8	8.5	2.4
Reduction <50%	15.4	4.8	16.1	4.1
Reduction from 50% to < 100%	21.3	6.2	22.2	5.4
Complete withdrawal***	26.5	7.7	27.3	7.2
ACT questionnaire[&]: change relative to baseline				
Decrease ≥ 2 points[17]	0.0	0.0	0.0	0.0
No change (increase <2 or decrease < 2 points)	4.8	2.8	4.8	2.8
Increase ≥2 points and total score ≤19[19]	9.1	4.8	9.1	4.9
Increase ≥2 points and total score 20 to <23[17]	12.9	6.2	12.8	6.4
Increase ≥ 2 points and total score ≥ 23	16.4	7.7	16.0	8.1
On treatment FEV_1[◊]: change relative to the predicted FEV_1 value at baseline				
Decrease ≥10%[16]	0.0	0.0	0.0	0.0
No change (decrease <10% or increase <10%)	4.4	3.3	4.5	3.6
Increase from 10% to <15%	7.9	5.4	8.0	5.7
Increase from 15% to <20%	10.3	6.3	10.3	6.6
Increase ≥20%	12.2	7.0	12.1	7.4
PAQLQ questionnaire^: change relative to baseline				
Decrease ≥ 0.5 points[21]	0.0	0.0	0.0	0.0
No change (increase < 0.5 or decrease < 0.5 points)	3.0	1.9	3.2	1.9
Increase ≥ 0.5 points and total score < 5	6.0	3.4	6.3	3.4
Increase ≥ 0.5 points and total score 5 to < 6	9.0	4.6	9.3	4.7
Increase ≥ 0.5 points and total score ≥ 6	11.	6.1	12.2	6.3

B. Adult CONFiRM

	All participants (n=63)		Participants answered 2 scenarios consistently (n=49)	
	Mean weight, %	SD	Mean weight, %	SD
Severe asthma attacks:[5,24] change relative to previous 12 months				
Increase[#]	0.0	0.0	0.0	0.0
No change[##]	10.1	3.7	10.5	3.5
Reduction <50%	19.0	6.0	19.6	5.8
Reduction from 50% to < 100%	26.3	7.0	26.9	7.1
100% reduction	32.4	8.2	32.9	8.4
Maintenance OCS dose for asthma:[5] change relative to baseline				
Increase*	0.0	0.0	0.0	0.0
No change**	8.6	3.5	8.7	3.7
Reduction <50%	16.1	5.8	16.2	6.1
Reduction from 50% to < 100%	22.1	6.9	22.4	7.2
Complete withdrawal***	27.3	8.1	27.7	8.5
SAQ questionnaire[&]: change relative to baseline				
Decrease ≥ 0.5 points[22]	0.0	0.0	0.0	0.0
No change (increase <0.5 or decrease <0.5 points)	4.3	3.0	4.2	3.0
Increase ≥0.5 points and total score <5	8.1	6.8	8.0	4.9
Increase ≥0.5 points and total score 5 to <6	11.5	5.2	11.5	7.0
Increase ≥0.5 points and total score ≥6	14.6	9.0	14.7	9.6
ACQ-5 questionnaire[^]: change relative to baseline				
Increase ≥0.5 points[18]	0.0	0.0	0.0	0.0
No change (increase <0.5 or decrease <0.5 points)	3.6	2.1	3.6	1.9
Decrease ≥0.5 points and total score >1.5[20]	7.1	3.6	7.0	3.1
Decrease ≥0.5 points and total score from >0.75 to 1.5	10.3	4.5	10.0	3.8
Decrease ≥0.5 points and total score ≤0.75[20]	13.4	5.6	12.8	4.8
On treatment FEV_1[◊]: change relative to the predicted FEV_1 value at baseline				
Decrease ≥10%[16]	0.0	0.0	0.0	0.0
No change (decrease <10% or increase <10%)	4.3	2.9	4.3	2.9
Increase from 10% to <15%	7.8	5.9	7.7	4.9
Increase from 15% to <20%	10.3	4.9	10.1	6.0
Increase ≥20%	12.3	6.5	11.8	6.6

Figures represent weights (as points) for each COMSA outcome by level. These weights were generated by the 1000minds software and used to generate the composite score with an adjustment made to centre non-response on zero. Weights are raw data from 1000minds before the score was re-scaled so that 0 represented no change. Please see further footnotes in Table S3. Consistent choice is defined as reporting the same response (patient 1 improved most, patient 2 improved most or 'they are the same'). ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; CONFiRM, CompOsite iNdex For Response in asthMa; FEV_1, forced expiratory volume in 1 second; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; OCS, oral corticosteroids; SAQ, Severe Asthma Questionnaire.

Table S8. Weights of outcome measures from 1000Mind software assigned by patient advocates and healthcare professionals who did and did not consistently answer two repeated scenarios (step 2)

A. Paediatric CONFiRM

	Patient advocates, mean weights %		Healthcare professionals, mean weights %	
	All (n=20)	Consistently answered (n=15)	All (n=46)	Consistently answered (n=39)
Severe asthma attacks:[5,24] change relative to previous 12 months				
Increase[#]	0.0	0.0	0.0	0.0
No change[##]	9.6	9.4	10.9	10.7
Reduction <50%	17.9	17.5	20.5	20.1
Reduction from 50% to < 100%	24.3	23.6	28.1	27.6
100% reduction	29.5	28.4	34.5	33.9
Maintenance OCS dose for asthma:[5] change relative to baseline				
Increase*	0.0	0.0	0.0	0.0
No change**	7.8	8.7	8.3	8.5
Reduction <50%	14.7	16.1	15.7	16.1
Reduction from 50% to < 100%	20.2	21.8	21.8	22.3
Complete withdrawal***	25.0	26.5	27.2	27.7
ACT questionnaire[&]: change relative to baseline				
Decrease ≥ 2 points[17]	0.0	0.0	0.0	0.0
No change (increase <2 or decrease < 2 points)	5.1	4.9	4.6	4.8
Increase ≥2 points and total score ≤19[19]	9.8	9.2	8.9	9.1
Increase ≥2 points and total score 20 to <23[17]	13.6	12.8	12.6	12.7
Increase ≥ 2 points and total score ≥ 23	17.0	16.0	16.1	16.0
PAQLQ questionnaire^: change relative to baseline				
Decrease ≥ 0.5 points[21]	0.0	0.0	0.0	0.0
No change (increase < 0.5 or decrease < 0.5 points)	3.7	4.4	2.7	2.8
Increase ≥ 0.5 points and total score < 5	7.5	8.7	5.4	5.4
Increase ≥ 0.5 points and total score 5 to < 6	11.3	12.7	8.0	8.0
Increase ≥ 0.5 points and total score ≥ 6	15.0	16.5	10.5	10.5
On treatment FEV_1[◊]: change relative to the predicted FEV_1 value at baseline				
Decrease ≥10%[16]	0.0	0.0	0.0	0.0
No change (decrease <10% or increase <10%)	5.2	5.2	4.1	4.2
Increase from 10% to <15%	9.1	8.9	7.4	7.6
Increase from 15% to <20%	11.6	11.1	9.8	10.0
Increase ≥20%	13.4	12.6	11.7	11.9

B. Adult CONFiRM

	Patient advocates, mean weights %		Healthcare professionals, mean weights %	
	All (n=20)	Consistently answered (n=15)	All (n=42)	Consistently answered (n=34)
Severe asthma attacks:[5,24] change relative to previous 12 months				
Increase[#]	0.0	0.0	0.0	0.0
No change[##]	9.0	9.0	10.6	11.1
Reduction <50%	17.2	17.3	19.9	20.6
Reduction from 50% to < 100%	24.1	24.4	27.3	27.9
100% reduction	30.1	30.8	33.6	33.9
Maintenance OCS dose for asthma:[5] change relative to baseline				
Increase*	0.0	0.0	0.0	0.0
No change**	7.6	7.7	9.1	9.1
Reduction <50%	14.4	14.7	16.9	16.9
Reduction from 50% to < 100%	20.0	20.8	23.1	23.1
Complete withdrawal***	24.9	26.2	28.4	28.4
SAQ questionnaire[&]: change relative to baseline				
Decrease ≥ 0.5 points[22]	0.0%	0.0%	0.0%	0.0
No change (increase <0.5 or decrease <0.5 points)	4.7%	4.2%	4.1%	4.2
Increase ≥0.5 points and total score <5	9.2%	8.6%	7.6%	7.8
Increase ≥0.5 points and total score 5 to <6	13.8%	13.5%	10.4%	10.6
Increase ≥0.5 points and total score ≥6	18.5%	18.6%	12.7%	13.0
ACQ-5 questionnaire[^]: change relative to baseline				
Increase ≥0.5 points[18]	0.0	0.0	0.0	0.0
No change (increase <0.5 or decrease <0.5 points)	2.9	3.1	4.0	3.9
Decrease ≥0.5 points and total score >1.5[20]	6.0	6.2	7.7	7.4
Decrease ≥0.5 points and total score from >0.75 to 1.5	9.4	9.2	10.8	10.4
Decrease ≥0.5 points and total score ≤0.75[20]	13.0	12.3	13.6	13.0
On treatment FEV_1[◊]: change relative to the predicted FEV_1 value at baseline				
Decrease ≥10%[16]	0.0	0.0	0.0	0.0
No change (decrease <10% or increase <10%)	4.6	4.3	4.2	4.3
Increase from 10% to <15%	8.3	7.7	7.6	7.7
Increase from 15% to <20%	11.1	10.2	10.0	10.1
Increase ≥20%	13.4	12.1	11.7	11.7

Figures represent weights (as points) for each COMSA outcome by level. These weights were generated by the 1000minds software and used to generate the composite score with an adjustment made to centre non-response on zero. These weights are raw data from before the score was re-scaled so that 0 represented no change. Please see further footnotes in Table S3. Consistent choice is defined as reporting the same response (patient 1 improved most, patient 2 improved most or 'they are the same'). ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; CONFiRM, CompOsite iNdex For Response in asthMa; FEV_1, forced expiratory volume in 1 second; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; OCS, oral corticosteroids; SAQ, Severe Asthma Questionnaire.

Table S9. Mean maximal preference weight from 1000Mind software with and without participants who answered repeated scenarios differently (step 2)

A. Paediatric CONFiRM

	Total n=66	Participants who answered two repeated scenarios differently excluded, n=65	Participants who answered one or both repeated scenarios differently excluded, n=54
	Mean weight (SD) %		
Severe asthma attacks	33.0 (8.9)	32.9 (9.0)	32.4 (8.9)
Maintenance OCS dose for asthma	26.5 (7.8)	26.7 (7.6)	27.3 (7.2)
ACT questionnaire	16.4 (7.7)	16.3 (7.7)	16.0 (8.1)
PAQLQ questionnaire	11.9 (6.1)	11.9 (6.1)	12.2 (6.3)
On treatment FEV_1	12.2 (7.0)	12.2 (7.1)	12.1 (7.3)

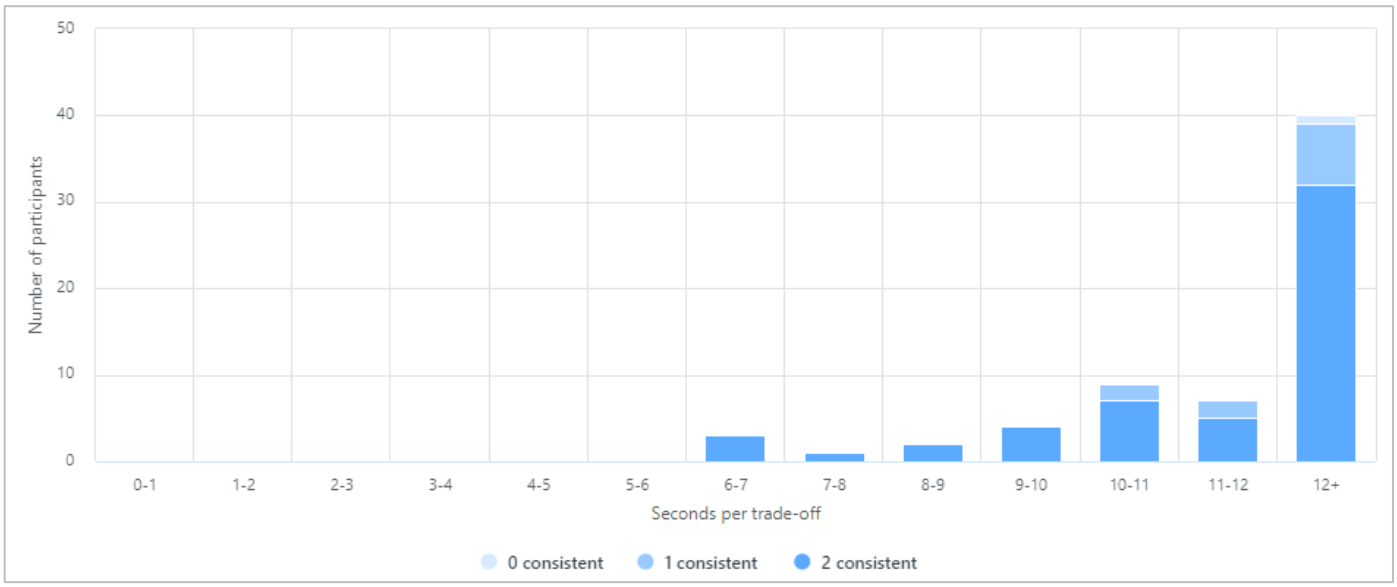
B. Adult CONFiRM

	Total n=63	Participants who answered two repeated scenarios differently excluded, n=61	Participants who answered one or both repeated scenarios differently excluded, n=49
	Mean weight (SD) %		
Severe asthma attacks	32.4 (8.2)	32.5 (8.2)	32.9 (8.4)
Maintenance OCS dose for asthma	27.3 (8.1)	27.4 (8.2)	27.7 (8.5)
SAQ questionnaire	14.6 (9.0)	14.6 (9.2)	14.7 (9.6)
ACQ-5 questionnaire	13.4 (5.6)	13.1 (5.3)	12.8 (4.8)
On treatment FEV_1	12.3 (6.5)	12.4 (6.5)	11.8 (6.6)

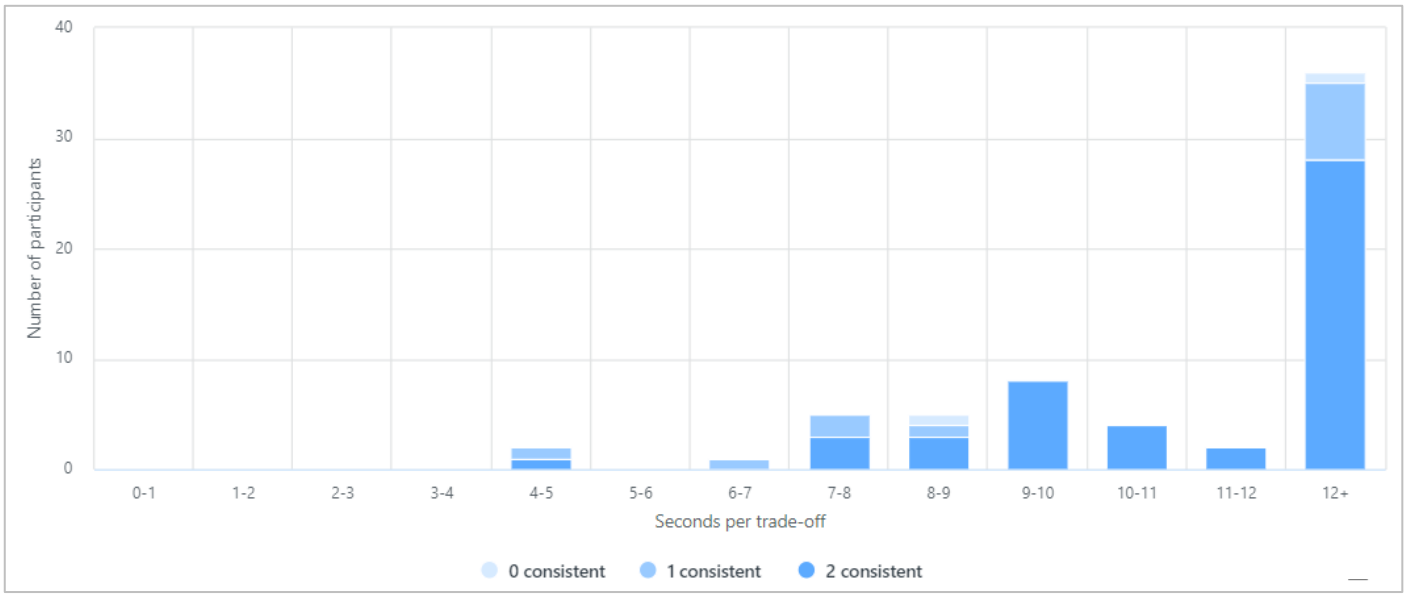
Figures are means (standard deviations) maximal preference weight from 1000Mind software from step 2. The consistency of each participant's choices was tested by repeating two previously answered scenarios. Consistent is defined by reporting the same response (patient 1 over patient 2 or 'they are the same'). Weights are raw data from before the score was re-scaled so that 0 represented no change. Severe asthma attacks are defined as per ATS/ERS guideline.[23] Maintenance oral corticosteroid use is defined as daily or alternate day use of oral corticosteroids. ACT, Asthma Control Test; FEV_1, forced expiratory volume in 1 second; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; OCS, oral corticosteroids. ACQ, Asthma Control Questionnaire; CONFiRM, CompOsite iNdex For Response in asthMa; FEV_1, percent predicted forced expiratory volume in 1 second; OCS, oral corticosteroids; SAQ, Severe Asthma Questionnaire.

Figure S2. Median time taken to answer scenarios by all participants (step 2)

A. Paediatric CONFiRM



B. Adult CONFiRM



Bars represent number of participants. The consistency of each participant's choices was tested by repeating two previously answered scenarios. Consistent choice is defined as reporting the same response (patient 1 improved most, patient 2 improved most or 'they are the same'). CONFiRM, CompOsite iNdex For Response in asthMa.

Table S10. Additional questions for survey participants (step 2)

A. All participants

	Paediatric survey			Adult survey		
	Total (n=66)	Patient advocates (n=20)	Healthcare professionals (n=46)	Total (n=63)	Patient advocates (n=21)	Healthcare professionals (n=42)
Does this order seem about right to you, n (%)						
Yes	47 (71.2%)	16 (80.0%)	31 (67.4%)	53 (84.1%)	20 (95.2%)	33 (78.6%)
No	19 (28.8%)	4 (20.0%)	15 (32.6%)	10 (15.9%)	1 (4.8%)	9 (21.4%)
How did you find understanding the survey instructions/ design? n (%)						
Very easy	19 (28.8%)	4 (20.0%)	15 (32.6%)	18 (28.6%)	6 (28.6%)	12 (28.6%)
Easy	30 (45.5%)	11 (55.0%)	19 (41.3%)	25 (39.7%)	8 (38.1%)	17 (40.5%)
Neutral	11 (16.7%)	3 (15.0%)	8 (17.4%)	15 (23.8%)	6 (28.6%)	9 (21.4%)
Difficult	6 (9.1%)	2 (10.0%)	4 (8.7%)	5 (7.9%)	1 (4.8%)	4 (9.5%)
Very difficult	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (100.0%)	0 (100.0%)

B. Restricted to participants who consistently answered two repeated scenarios.

	Paediatric survey			Adult survey		
	Total (n=54)	Patient advocates (n=15)	Healthcare professionals (n=39)	Total (n=49)	Patient advocates (n=15)	Healthcare professionals (n=34)
Does this order seem about right to you, n (%)						
Yes	38 (70.4%)	12 (80.0%)	26 (66.7%)	42 (85.7%)	15 (100.0%)	27 (79.4%)
No	16 (29.6%)	3 (20.0%)	13 (33.3%)	7 (14.3%)	0 (0.0%)	7 (20.6%)
How did you find understanding the survey instructions/ design? n (%)						
Very easy	16 (29.6%)	3 (20.0%)	13 (33.3%)	15 (30.6%)	5 (33.3%)	10 (29.4%)
Easy	25 (46.3%)	8 (53.3%)	17 (43.6%)	21 (42.9%)	7 (46.7%)	14 (41.2%)
Neutral	9 (16.7%)	2 (13.3%)	7 (17.9%)	10 (20.4%)	3 (20.0%)	7 (20.6%)
Difficult	4 (7.4%)	2 (13.3%)	2 (5.1%)	3 (6.1%)	0 (100.0%)	3 (8.8%)
Very difficult	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (6.1%)	0 (100.0%)	0 (0.0%)

Figures represent number (percentage) of participants. The consistency of each participant's choices was tested by repeating two previously answered scenarios. Consistent choice is defined as reporting the same response (patient 1 improved most, patient 2 improved most or 'they are the same'). Final order of the outcome measures was based on individual participants' ranking of patient pairs only.

Table S11. Weights of outcome measures depending on the expectation of the results assigned by all participants and participants who consistently answered 2 repeated scenarios (step 2)

A. Paediatric CONFiRM

	All participants, mean weights %			Restricted to participants who consistently answered repeated scenarios, mean weights %		
	Does this order seem about right to you?		Total (n=66)	Does this order seem about right to you?		Total (n=54)
	Yes (n=47)	No (n=19)		Yes (n=38)	No (n=16)	
Severe asthma attacks:[5,24] change relative to previous 12 months						
Increase[#]	0.0	0.0	0.0	0.0	0.0	0.0
No change[##]	10.8	9.6	10.5	10.7	9.5	10.3
Reduction <50%	27.6	25.4	27.0	19.9	18.0	19.4
Reduction from 50% to < 100%	20.3	18.2	19.7	27.1	25.1	26.5
100% reduction	33.6	31.5	33.0	32.9	31.1	32.4
Maintenance OCS dose for asthma:[5] change relative to baseline						
Increase*	0.0	0.0	0.0	0.0	0.0	0.0
No change**	7.9	8.7	8.1	8.3	9.1	8.5
Reduction <50%	15.2	15.9	15.4	15.8	16.6	16.1
Reduction from 50% to < 100%	21.4	21.1	21.3	22.1	22.2	22.2
Complete withdrawal***	27.0	25.2	26.5	27.6	26.6	27.3
ACT questionnaire[&]: change relative to baseline						
Decrease ≥ 2 points[17]	0.0	0.0	0.0	0.0	0.0	0.0
No change (increase <2 or decrease < 2 points)	5.0	4.2	4.8	5.3	3.7	4.8
Increase ≥2 points and total score ≤19[19]	9.5	8.2	9.1	9.9	7.3	9.1
Increase ≥2 points and total score 20 to <23[17]	13.4	11.9	12.9	13.6	10.7	12.8
Increase ≥ 2 points and total score ≥ 23	16.8	15.5	16.4	16.8	14.1	16.0
On treatment FEV_1[◊]: change relative to the predicted FEV_1 value at baseline						
Decrease ≥10%[16]	0.0	0.0	0.0	0.0	0.0	0.0
No change (decrease <10% or increase <10%)	3.8	5.9	4.4	3.7	6.4	4.5
Increase from 10% to <15%	6.8	10.7	7.9	6.6	11.4	8.0
Increase from 15% to <20%	8.8	14.2	10.3	8.4	14.9	10.3
Increase ≥20%	10.4	16.9	12.2	9.9	17.4	12.1
PAQLQ questionnaire^: change relative to baseline						
Decrease ≥ 0.5 points[21]	0.0	0.0	0.0	0.0	0.0	0.0
No change (increase < 0.5 or decrease < 0.5 points)	3.0	3.0	3.0	3.2	3.3	3.2
Increase ≥ 0.5 points and total score < 5	6.1	5.8	6.0	6.4	6.2	6.3
Increase ≥ 0.5 points and total score 5 to < 6	9.2	8.4	9.0	9.6	8.6	9.3
Increase ≥ 0.5 points and total score ≥ 6	12.3	10.9	11.9	12.8	10.8	12.2

B. Adult CONFiRM

	All participants, mean weights %			Restricted to participants who consistently answered repeated scenarios, mean weights %		
	Does this order seem about right to you?		Total (n=63)	Does this order seem about right to you?		Total (n=49)
	Yes (n=53)	No (n=10)		Yes (n=42)	No (n=7)	
Severe asthma attacks:[5,24] change relative to previous 12 months						
Increase[#]	0.0	0.0	0.0	0.0	0.0	0.0
No change[##]	10.1	9.9	10.1	10.4	11.1	10.5
Reduction <50%	19.1	18.6	19.0	19.4	20.9	19.6
Reduction from 50% to < 100%	26.4	25.6	26.3	26.6	28.7	26.9
100% reduction	32.6	31.5	32.4	32.6	35.2	32.9
Maintenance OCS dose for asthma:[5] change relative to baseline						
Increase*	0.0	0.0	0.0	0.0	0.0	0.0
No change**	8.3	10.1	8.6	8.4	10.5	8.7
Reduction <50%	15.7	18.0	16.1	15.8	18.6	16.2
Reduction from 50% to < 100%	21.9	23.0	22.1	22.1	24.0	22.4
Complete withdrawal***	27.4	26.7	27.3	27.6	28.1	27.7
SAQ questionnaire[&]: change relative to baseline						
Decrease ≥ 0.5 points[22]	0.0	0.0	0.0	0.0	0.0	0.0
No change (increase <0.5 or decrease <0.5 points)	4.1	5.3	4.3	4.2	4.3	4.2
Increase ≥0.5 points and total score <5	7.9	9.4	8.1	8.1	7.8	8.0
Increase ≥0.5 points and total score 5 to <6	11.5	11.8	11.5	11.7	10.2	11.5
Increase ≥0.5 points and total score ≥6	14.9	13.3	14.6	15.2	12.1	14.7
ACQ-5 questionnaire[^]: change relative to baseline						
Increase ≥0.5 points[18]	0.0	0.0	0.0	0.0	0.0	0.0
No change (increase <0.5 or decrease <0.5 points)	3.5	4.2	3.6	3.7	3.3	3.6
Decrease ≥0.5 points and total score >1.5[20]	6.9	8.2	7.1	7.2	6.3	7.0
Decrease ≥0.5 points and total score from >0.75 to 1.5	10.0	12.0	10.3	10.2	9.0	10.0
Decrease ≥0.5 points and total score ≤0.75[20]	13.0	15.7	13.4	13.0	11.5	12.8
On treatment FEV_1[◊]: change relative to the predicted FEV_1 value at baseline						
Decrease ≥10%[16]	0.0	0.0	0.0	0.0	0.0	0.0
No change (decrease <10% or increase <10%)	4.2	4.5	4.3	4.1	5.3	4.3
Increase from 10% to <15%	7.8	8.2	7.8	9.8	11.9	10.1
Increase from 15% to <20%	10.3	10.9	10.3	7.5	9.5	7.7
Increase ≥20%	12.2	12.8	12.3	11.6	13.2	11.8

Figures represent weights (as points) for each COMSA outcome by level. These weights were generated by the 1000minds software and used to generate the composite score with an adjustment made to centre non-response on zero. Please see further footnotes in **Table S3.** The consistency of each participant's choices was tested by repeating two previously answered scenarios. Consistent choice is defined as reporting the same response (patient 1 improved most, patient 2 improved most or 'they are the same'). Final order of the outcome measures was based on individual participants' ranking of patient pairs only. ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; FEV1, CONFiRM, CompOsite iNdex For Response in asthMa; forced expiratory volume in 1 second; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; OCS, oral corticosteroids. SAQ, Severe Asthma Questionnaire.

Appendix 11. Step 3 results: Assess internal validity of CONFiRM scores

A total of 50 paediatric patient profiles and 50 adult profiles were utilised in the internal validation (step 3). We aimed to include the entire range of potential responses with these cases. A summary of the patient profiles included in step 3 can be found in **Table S12.**

A total of 146 participants were involved in step 3. For the paediatric profiles this included 45 (57.0%) HCPs and 34 (43.0%) patient advocates. For the adult profiles, this included 44 (65.7%) HCP and 23 (34.3%) patient advocates (**Table S13**). Representatives from 28 countries took part, approximately 57% HCPs were adult or paediatric pulmonologists, and 60% of patient advocates had currently been prescribed biologics (**Table S13**).

Figure S3 describes how patient advocates and HCPs classified overall response to biological for each patient profile. These would appear to be very similar. Two patient profiles were repeated in each of the paediatric and adult sets (asterix in **Figure S3**). Agreement on assigned overall magnitude of response for repeated profiles was moderate for individual participants for the adult patients (**Table S14**). Intraclass correlation coefficient (ICC) for agreement between the repeated profiles were 0.79 (95% confidence interval 0.58 to 0.90) and 0.65 (0.29 to 0.83) for patient advocates and 0.84 (0.70 to 0.92) and 0.55 (0.16 to 0.76) for HCPs. For repeated paediatric profiles, agreement was moderate for HCP but very low for patient advocates for the paediatric patients (**Table S15**) – ICC for agreement between repeast profiles were 0.10 (-1.31 to 0.63) and -0.15 (-2.11 to 0.55) for patient advocates and 0.61 (0.29 to 0.79 and 0.60 (0.26 to 0.79) for HCPs.

Table S15 describes how the median CONFIRM scores change with each overall magnitude of response. The CONFiRM scores clearly increases with each increase in overall magnitude of response for both the paediatric and adult scores (**Figure 4**). The CONFiRM scores for each overall magnitude of change were significantly different for both the paediatric (Kruskal-Willis $\chi2= 2623.1$, $p<0.05$; $\chi2=2506.5$, $p<0.05$; $\chi2= 2657.1$, $p<0.05$ for all participants, patient advocates and HCP respectively) and adult CONFiRM ($\chi2= 2974.7$, $p<0.05$; $\chi2= 2854.3$, $p<0.05$; $\chi2= 3216.3$, $p<0.05$)(**Figure 4**). Similar results were found for patient profiles where mOCS was not used at baseline (**Figure S4**).

Figures S5 and S6 describe the ability of the CONFiRM scores to distriminate between achieving /not achieving a substantial response and achieving / not achieving a sufficient response respectively. The composite measures had excellent discriminative ability for substantial response as compared with less than substantial response for paediatric (area under the curve (AUC) 0.99 (95% CI 0.99, 0.99)) and adult CONFiRM (0.95 (95% CI 0.95; 0.96)). This was also the case for sufficient response as compared with less than sufficient response (paediatric 0.99 (95% CI 0.99, 0.99); adult 0.92 (95% CI 0.91, 0.92)) **(Figure S5-S6).** Results were similar for

HCPs and patient advocates, whether on or off mOCS at baseline **(Table S16).** An additional bootstrap analysis to reduce an overfitting, gave similar results (**Table S16**).

Figure S7 compares the adult CONFiRM score with the published FEOS [5] response score. We found a high level of correlation between them using either a 0.75 and 1.5 ACQ-5 cut offs ((r=0.93 and r=0.92 respectively, both p<0.001). The adult CONFiRM also demonstrated good discrimination for super-responders as per the Delphi super-responder definition (AUC 0.93 (95 CI% 0.92-0.94), p<0.001) (**Figure S8**).

A total of 75 participants attended the stakeholder meetings to discuss the results of the internal validation. This included 48 (64.0%) HCPs, 19 (25.3%) patient advocates, 5 (6.7%) pharmaceutical representatives, 2 (2.7%) health regulators and one (1.3%) representative from the 1000minds team. Several comments for improvement of the CONFiRM tools were suggested and implemented (**Table S17**). These included suggestions about some additional sensitivity analyses, weighting patient profiles in the analysis according to their frequency in the original patient dataset, rescaling the CONFiRM so that 0 represented no response and using bootstrapping to adjust for any overfitting.

Table S12. Description of patient profiles included in step 3.

	Paediatric profiles (n=50)		Adult profiles (n=50)	
	Baseline	1 year follow up	Baseline	1 year follow up
Age, median (IQR)	12.0 (9.0, 14.0)	NA	49 (38.5, 58.0)	NA
Gender Female, n (%)	24 (48.0)		27 (54.0)	
Biological therapy, n (%) Dupilumab Benralizumab Mepolizumab Omalizumab	0 (0.0) 0 (0.0) 5 (10.0) 45 (90.0)		8 (16.0) 1 (2.0) 12 (24.0) 29 (58.0)	
Severe asthma attacks, median (IQR)	10.0 (10.0, 14.0)	0.5 (0.0, 5.3)	6.0 (2.8, 7.3)	2.0 (0.0, 3.0)
Maintenance OCS, n (%)	13 (26.0)	3 (6.0)	21 (42.0)	20 (40.0)
Maintenance OCS dose, mg (IQR)	NI	NI	10.0 (5.0, 10.0)	7.5 (5.0, 10.0)
On treatment FEV_1, median (IQR) %	83.5 (69.8, 96.0)	86.5 (75.3, 97.0)	66.8 (51.8, 82.1)	73.0 (50.8, 89.0)
SAQ, median (IQR), points	NA	NA	3.5 (3.1, 4.1)	4.0 (3.6, 4.3)
PAQLQ, median (IQR), points	5.5 (3.8, 6.4)	6.1 (5.0, 6.3)	NA	NA
ACT, median (IQR), points	15.0 (9.0, 20.0)	18.0 (13.0, 21.3)	NA	NA
C-ACT, median (IQR), points	15.5 (10.8, 17.0)	20.0 (15.0, 22.0)	NA	NA
ACQ-5, median (IQR), points	NA	NA	3.0 (2.4; 4.0)	1.9 (0.8; 3.6)
Overall magnitude of change*, n (%) Deleterious No change		7 (14.0) 5 (10.0)		5 (10.0) 12 (24.0)

Sufficient response		5 (10.0)		7 (14.0)
Substantial response		19 (38.0)		20 (40.0)
Super-response		14 (28.0)		6 (12.0)

Table summarises the description of patient profiles used in the step 3. *Overall magnitude of change (box 1) according to rating of HCPs and patient advocates. Severe asthma attacks are defined as per ATS/ERS guideline.[23] Maintenance oral corticosteroid use is defined as daily or alternate day use of oral corticosteroids. Patient profiles were selected based on clustering analysis of the total dataset of 2,011 patients. ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Test; COMSA, Core Outcome Measures sets for paediatric and adult severe asthma; IOR, interquartile range; FEV_1, percent predicted forced expiratory volume in 1 second; NA, not applicable; NI no information; OCS, oral corticosteroids; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; SAQ, Severe Asthma Questionnaire.

Table S13. Overall demographic information about step 3 participants

A. All participants

	Paediatric profiles, n (%)		Adult profiles, n (%)	
	Healthcare professionals n=44	Patient advocates n=23	Healthcare professionals n=45	Patient advocates n=34
Country				
United Kingdom	12 (27.3)	6 (26.1)	15 (33.3)	10 (29.4)
Sweden	3 (6.8)	4 (17.4)	3 (6.7)	5 (14.7)
Netherlands	4 (9.1)	3 (13.0)	3 (6.7)	3 (8.8)
Italy	4 (9.1)	1 (4.3)	1 (2.2)	3 (8.8)
Canada	2 (4.5)	1 (4.3)	3 (6.7)	1 (2.9)
France	4 (9.1)	1 (4.3)	2 (4.4)	0 (0.0)
United States	0 (0.0)	4 (17.4)	1 (2.2)	2 (5.9)
Belgium	0 (0.0)	2 (8.7)	1 (2.2)	3 (8.8)
Denmark	1 (2.3)	0 (0.0)	1 (2.2)	2 (5.9)
Germany	2 (4.5)	0 (0.0)	1 (2.2)	1 (2.9)
Spain	3 (6.8)	0 (0.0)	0 (0.0)	1 (2.9)
Australia	0 (0.0)	0 (0.0)	3 (6.7)	0 (0.0)
Other*	9 (20.5)	1 (4.3)	10 (22.2)	3 (8.8)
Gender				
Male	23 (52.3)	7 (30.4)	25 (55.6)	9 (26.5)
Female	21 (47.7)	16 (69.6)	20 (44.4)	25 (73.5)
Age group, years				
12-17	0 (0.0)	2 (8.7)	0 (0.0)	0 (0.0)
18-25	0 (0.0)	2 (8.7)	0 (0.0)	5 (14.7)
26-36	1 (2.3)	3 (13.0)	2 (4.4)	5 (14.7)
37-47	6 (13.6)	4 (17.4)	10 (22.2)	8 (23.5)
48-58	17 (38.6)	7 (30.4)	15 (33.3)	11 (32.4)
59-69	14 (31.8)	3 (13.0)	13 (28.9)	3 (8.8)
70-80	6 (13.6)	2 (8.7)	5 (11.1)	2 (5.9)

B. Demographic information about patient advocates

Patient representatives	Paediatric profiles, n (%) n=23	Adult profiles, n (%) n=34
During the last year I had		
Two or more courses of systemic corticosteroids for asthma	6 (28.6)	13 (40.6)
Treatment daily or every other day with systemic corticosteroids for asthma	7 (33.3)	11 (34.4)
An emergency hospital admission or ED admission due to asthma	4 (19.0)	7 (21.9)
None of the above	6 (31.6)	12 (37.5)
Treatment with a biologic for asthma		
Yes, previously taken a biologic	2 (9.5)	5 (15.6)
Yes, currently taking a biologic	12 (57.1)	22 (68.8)
No	5 (23.8)	5 (15.6)
Prefer not to say	2 (9.5)	0 (0.0)
Switched from one to another biologic for asthma		
Yes	9 (64.3)	8 (29.6)
Duration of severe asthma, years		
Median (25^{th} -75^{th} percentile)	17 (13.0-41.0)	17.5 (10.5-35.0)
Other allergic conditions**		
Food allergy	11 (52.4)	17 (53.1)
Allergic rhinitis and/or conjunctivitis	15 (71.4)	21 (65.6)
Atopic dermatitis or eczema	6 (28.6)	11 (34.4)
Patient organisation representatives		
Duration of being a patient representative in the severe asthma field		
0-2 years	2 (50.0)	1 (50.0)
6-10 years	1 (25.0)	1 (50.0)
> 15 years	1 (25.0)	0 (0.0)

C. Demographic information about healthcare professionals

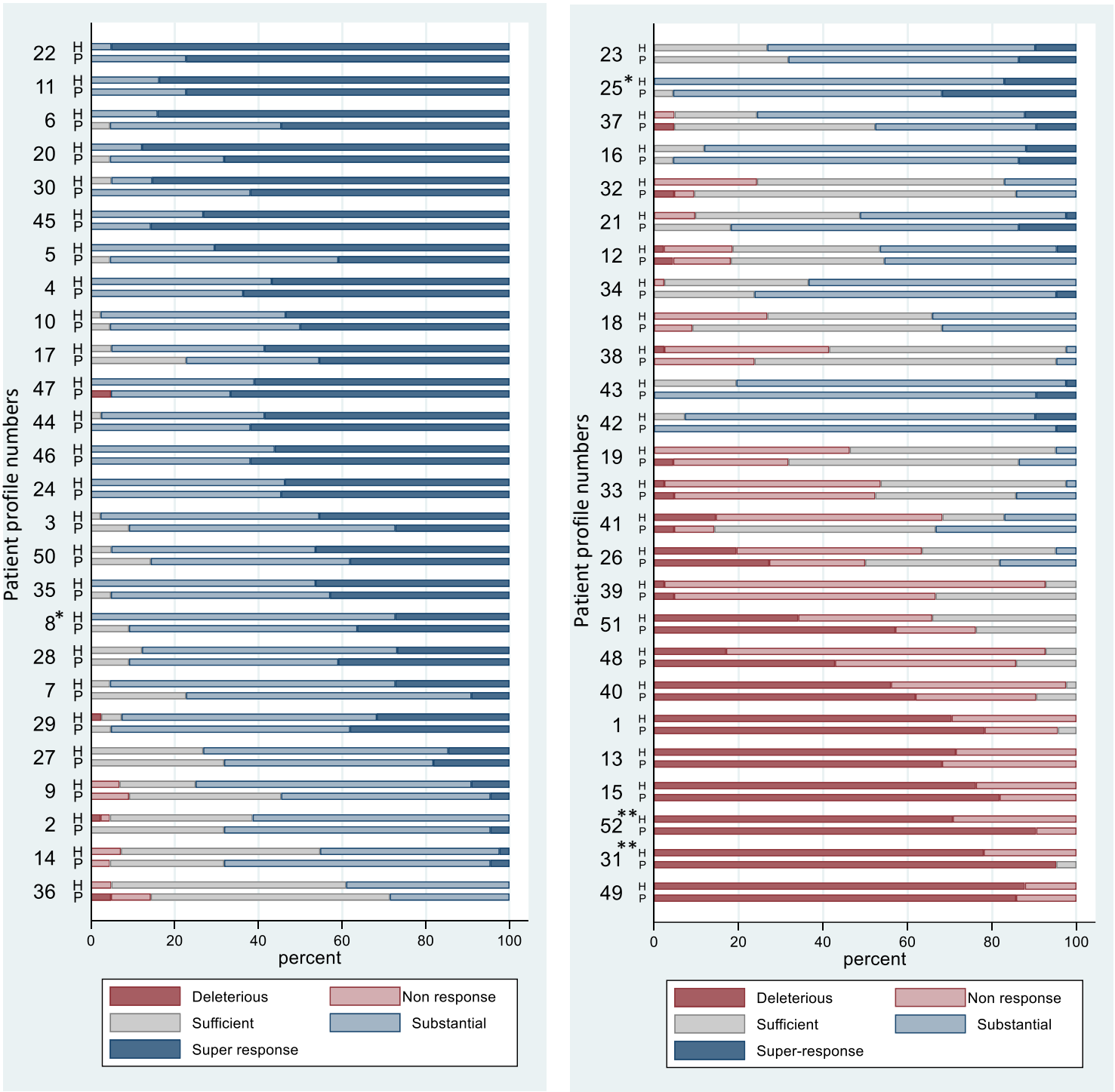
Healthcare professionals	Paediatric profiles, n (%) n=44	Adult profiles, n (%) n=45
Duration of treating patients with severe asthma		
0-5 years	3 (6.8)	2 (4.4)
5-10 years	2 (4.5)	8 (17.8)
10-20 years	18 (40.9)	14 (31.1)
Over 20 years	20 (45.5)	21 (46.7)
Not applicable	1 (2.3)	0 (0.0)
Advisory board, national/international severe asthma working group member in the past 5 years		
Yes	31 (70.5)	33 (73.3)
No	13 (29.5)	12 (26.7)
Author of a severe asthma and biologic publication in the past 5 years		
Yes	38 (86.4)	37 (82.2)
No	6 (13.6)	8 (17.8)
Practice setting		
Academic hospital/clinic	43 (97.7)	43 (95.6)
Non-academic hospital/clinic	1 (2.3)	2 (4.4)
Work in a specialist severe asthma unit		
Yes	36 (81.8)	38 (84.4)

No	1 (2.3)	7 (15.6)
Not applicable	7 (15.9)	0 (0.0)
Number of patients with severe asthma on biologics per year under care		
<5	4 (9.1)	0 (0.0)
5-10	15 (34.1)	2 (4.4)
11-20	12 (27.3)	2 (4.4)
21-50	9 (20.5)	12 (26.7)
51-100	2 (4.5)	8 (17.8)
101-200	0 (0.0)	10 (22.2)
>201	0 (0.0)	10 (22.2)
Not applicable	2 (4.5)	1 (2.2)
Speciality**		
Allergist	12 (27.3)	13 (28.9)
Pneumologist/ pulmonologist/ respiratory physician	25 (56.8)	35 (77.8)
Paediatrician	35 (79.5)	1 (2.2)
Asthma/Respiratory nurse	2 (4.5)	4 (8.9)
Clinical researcher	13 (29.5)	8 (17.8)
Pharmacist	0 (0.0)	1 (2.2)
Epidemiologist	1 (2.3)	0 (0.0)
Looking after		
Adults with severe asthma only (≥ 18 years)	1 (2.3)	40 (88.9)
Paediatric patients with severe asthma only (6-17years)	37 (84.1)	0 (0.0)
Both adult and paediatric patients with severe asthma	6 (13.6)	5 (11.1)

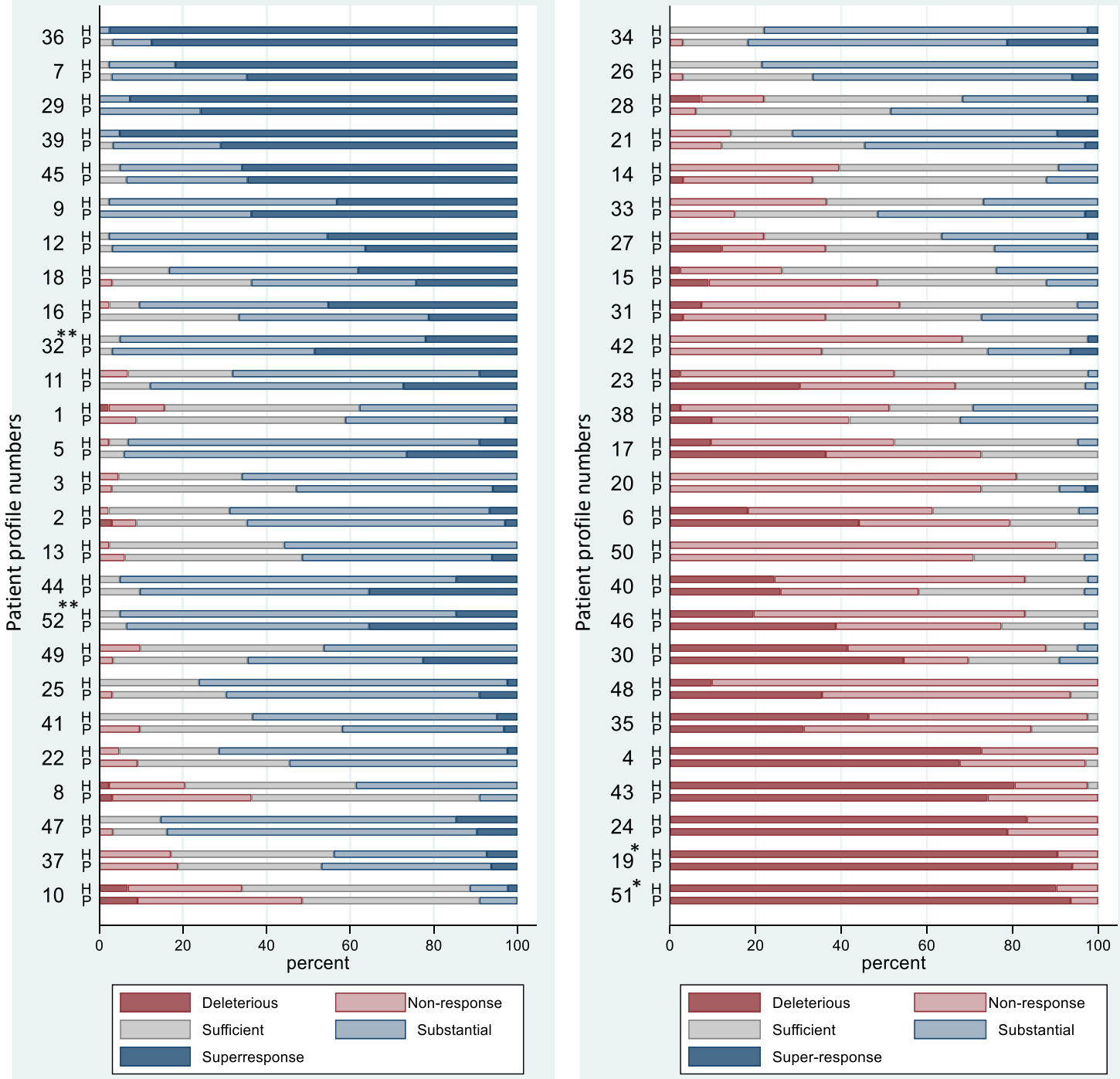
Figures represent number (percentage) of participants.*Other countries: Australia (n=3); Switzerland (n=3), China (n=2), Czech Republic (n=2), Finland (n=2), Poland (n=2), Romania (n=2), Turkey (n=2), Austria (n=1), Bulgaria (n=1), Croatia (n=1), Estonia (n=2), Japan (n=1), South Korea(n=1), Singapore(n=1), Slovenia(n=1). ** All answers that are applicable. Numbers represent count (percentage) unless otherwise indicated. ED, emergency department.

Figure S3. Agreement between patient advocates and healthcare professionals in classification of overall magnitude of response (step 3).

A. Paediatric survey



B. Adult survey



Figures show percentage of respondents classifying overall response to biological therapy as deleterious, non-response, sufficient, substantial or super-response. For each patient profile (numbered from 1 to 52), healthcare professional and patient advocate responses are adjacent to allow comparison. Response is ordered by magnitude in the healthcare professional group with the figure divided into two to allow it to fit on the page. For data quality, there were two repeated paediatric patient profiles: 8/25* and 31/52** and two adult patient profiles: 19/51* and 32/52**. H: Healthcare professionals; P: patient advocates.

Table S14. Participant responses for repeated patient profiles in step 3.

A. Repeated paediatric profiles

All participants (n, %)							
	Patient profile 25 (repeat of profile 8)						
		Deleterious	Non-	Sufficient	Substantial	Super-	*Total*
Patient profile 8	Deleterious	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Non-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Sufficient	0 (0.0)	0 (0.0)	0 (0.0)	**2 (100.0)**	0 (0.0)	*2 (100.0)*
	Substantial	0 (0.0)	0 (0.0)	0 (0.0)	**36 (85.7)**	**6 (14.3)**	*42 (100.0)*
	Super-	0 (0.0)	0 (0.0)	**1 (5.3)**	**10 (52.6)**	**8 (42.1)**	*19 (100.0)*
	Total	*0 (0.0)*	*0 (0.0)*	*1 (1.6)*	*48 (76.2)*	*14 (22.2)*	*63 (100.0)*
Healthcare professionals (n, %)							
	Patient profile 25 (repeat of profile 8)						
		Deleterious	Non-	Sufficient	Substantial	Super-	*Total*
Patient profile 8	Deleterious	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Non-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Sufficient	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Substantial	0 (0.0)	0 (0.0)	0 (0.0)	**28 (93.3)**	**2 (6.7)**	*30 (100.0)*
	Super-	0 (0.0)	0 (0.0)	0 (0.0)	**6 (54.5)**	**5 (45.5)**	*11 (100.0)*
	Total	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	*34 (82.9)*	*7 (17.1)*	*41 (100.0)*
Patient advocates (n, %)							
	Patient profile 25 (repeat of profile 8)						
		Deleterious	Non-	Sufficient	Substantial	Super-	*Total*
Patient profile 8	Deleterious	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Non-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Sufficient	0 (0.0)	0 (0.0)	0 (0.0)	**2 (100.0)**	0 (0.0)	*2 (100.0)*
	Substantial	0 (0.0)	0 (0.0)	0 (0.0)	**8 (66.7)**	**4 (33.3)**	*12 (100.0)*
	Super-	0 (0.0)	0 (0.0)	**1 (12.5)**	**4 (50.0)**	**3 (37.5)**	*8 (100.0)*
	Total	*0 (0.0)*	*0 (0.0)*	*1 (4.5)*	*14 (63.6)*	*7 (31.8)*	*22 (100.0)*

All participants (n, %)							
	Patient profile 52 (repeat of profile 31)						
		Deleterious	Non-	Sufficient	Substantial	Super-	*Total*
Patient profile 31	Deleterious	**44 (84.6)**	**8 (15.4)**	0 (0.0)	0 (0.0)	0 (0.0)	*52 (100.0)*
	Non	**3 (33.3)**	**6 (66.7)**	0 (0.0)	0 (0.0)	0 (0.0)	*9 (100.0)*
	Sufficient	**1 (100.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*1 (100.0)*
	Substantial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Super-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Total	*48 (77.4)*	*14 (22.6)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	*62 (100.0)*
Healthcare professionals (n, %)							
	Patient profile 52 (repeat of profile 31)						
		Deleterious	Non	Sufficient	Substantial	Super-	*Total*
Patient profile 31	Deleterious	**26 (81.3)**	**6 (18.7)**	0 (0.0)	0 (0.0)	0 (0.0)	*32 (100.0)*
	Non	**3 (33.3)**	**6 (66.7)**	0 (0.0)	0 (0.0)	0 (0.0)	*9 (100.0)*
	Sufficient	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Substantial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Super-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Total	*29 (70.7)*	*12 (29.3)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	*41 (100.0)*
Patient advocates (n, %)							
	Patient profile 52 (repeat of profile 31)						
		Deleterious	Non-	Sufficient	Substantial	Super-	*Total*

Patient profile 31	**Deleterious**	**18 (90.0)**	**2 (10.0)**	0 (0.0)	0 (0.0)	0 (0.0)	*20 (100.0)*
	Non-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Sufficient	**1 (100.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*1 (100.0)*
	Substantial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Super-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Total	*19 (90.5)*	*2 (9.5)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	*21 (100.0)*

B. Repeated adult profiles

All participants (n, %)							
	Patient profile 52 (repeat of profile 32)						
		Deleterious	**Non-**	**Sufficient**	**Substantial**	**Super-**	***Total***
Patient profile 32	**Deleterious**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Non-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Sufficient	0 (0.0)	0 (0.0)	**1 (33.3)**	**2 (66.6)**	0 (0.0)	*3 (100.0)*
	Substantial	0 (0.0)	0 (0.0)	**3 (6.6)**	**37 (82.2)**	**5 (11.1)**	*45 (100.0)*
	Super-	0 (0.0)	0 (0.0)	0 (0.0)	**12 (50.0)**	**12 (50.0)**	*24 (100.0)*
	Total	*0 (0.0)*	*0 (0.0)*	*4 (5.5)*	*51 (70.8)*	*17 (23.6)*	*72 (100.0)*
Healthcare professionals (n, %)							
	Patient profile 52 (repeat of profile 32)						
		Deleterious	**Non-**	**Sufficient**	**Substantial**	**Super-**	***Total***
Patient profile 32	**Deleterious**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Non-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Sufficient	0 (0.0)	0 (0.0)	0 (0.0)	**2 (100.0)**	0 (0.0)	*2 (100.0)*
	Substantial	0 (0.0)	0 (0.0)	**2 (6.7)**	**26 (86.7)**	**2 (6.7)**	*30 (100.0)*
	Super-	0 (0.0)	0 (0.0)	0 (0.0)	**5 (55.6)**	**4 (44.4)**	*9 (100.0)*
	Total	*0 (0.0)*	*0 (0.0)*	*2 (4.9)*	*33 (80.5)*	*6 (14.6)*	*41 (100.0)*
Patient advocates (n, %)							
	Patient profile 52 (repeat of profile 32)						
		Deleterious	**Non-**	**Sufficient**	**Substantial**	**Super-**	***Total***
Patient profile 32	**Deleterious**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Non-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Sufficient	0 (0.0)	0 (0.0)	**1 (100.0)**	0 (0.0)	0 (0.0)	*1 (100.0)*
	Substantial	0 (0.0)	0 (0.0)	**1 (6.7)**	**11 (73.3)**	**3 (20.0)**	*15 (100.0)*
	Super-	0 (0.0)	0 (0.0)	0 (0.0)	**7 (46.7)**	**8 (53.3)**	*15 (100.0)*
	Total	*0 (0.0)*	*0 (0.0)*	*2 (6.5)*	*18 (58.1)*	*11 (35.5)*	*31 (100.0)*

All participants (n, %)							
	Patient profile 51 (repeat of profile 19)						
		Deleterious	**Non-**	**Sufficient**	**Substantial**	**Super-**	***Total***
Patient profile 19	**Deleterious**	**65 (97.0)**	**2 (3.0)**	0 (0.0)	0 (0.0)	0 (0.0)	*67 (100.0)*
	Non	**1 (20.0)**	**4 (80.0)**	0 (0.0)	0 (0.0)	0 (0.0)	*5 (100.0)*
	Sufficient	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Substantial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Super-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Total	*66 (91.7)*	*6 (8.3)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	*72 (100.0)*
Healthcare professionals (n, %)							
	Patient profile 51 (repeat of profile 19)						
		Deleterious	**Non-**	**Sufficient**	**Substantial**	**Super-**	***Total***
Patient profile 19	**Deleterious**	**36 (97.3)**	**1 (2.7)**	0 (0.0)	0 (0.0)	0 (0.0)	*37 (100.0)*
	Non-	**1 (25.0)**	**3 (75.0)**	0 (0.0)	0 (0.0)	0 (0.0)	*4 (100.0)*
	Sufficient	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Substantial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Super-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Total	*37 (90.2)*	*4 (9.8)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	*41 (100.0)*

Patient advocates (n, %)							
	Patient profile 51 (repeat of profile 19)						
		Deleterious	Non-	Sufficient	Substantial	Super-	*Total*
Patient profile 19	**Deleterious**	**29 (96.7)**	**1 (3.3)**	0 (0.0)	0 (0.0)	0 (0.0)	*30 (100.0)*
	Non	0 (0.0)	**1 (100.0)**	0 (0.0)	0 (0.0)	0 (0.0)	*1 (100.0)*
	Sufficient	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Substantial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Super-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*
	Total	*29 (93.5)*	*2 (6.5)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	*31 (100.0)*

C. Intraclass correlation coefficient for repeated patient profiles (step 3).

	Paediatric survey ICC (95%CI)		Adult survey ICC (95%CI)	
	Profiles 8/25	**Profiles 31/52**	**Profiles 19/51**	**Profiles 32/52**
All participants	0.39 (-0.01 to 0.63)	0.49 (0.15 to 0.69)	0.83 (0.73 to 0.90)	0.63 (0.41 to 0.77)
Healthcare professionals	0.61 (0.29 to 0.79)	0.60 (0.26 to 0.79)	0.84 (0.70 to 0.92)	0.55 (0.16 to 0.76)
Patient advocates	0.10 (-1.31 to 0.63)	- 0.15 (-2.11 to 0.55)	0.79 (0.58 to 0.90)	0.65 (0.29 to 0.83)

Numbers in Tables A and B represent the number of participants (row percentage) rating each repeated profile at each level of overall magnitude of response to assess validity of responses. Intraclass correlation coefficient[14] (ICC) estimates and their 95% confident intervals in Table C were calculated using STATA software version 16.1 based on an absolute-agreement, 2-way mixed-effects model. ICC was used to calculate agreement between responses for the repeated patient profiles from all participants, patient advocates and HCPs. Values less than 0.5 are indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.90 indicate excellent reliability.

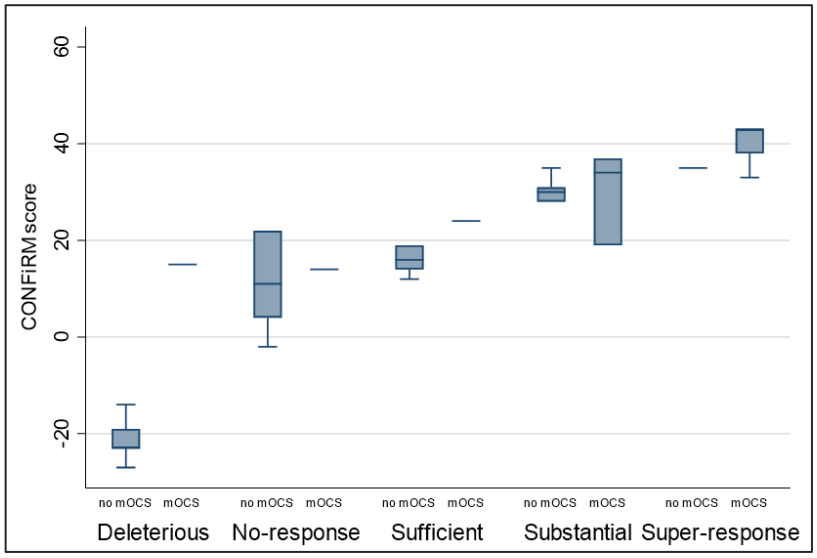
Table S15. Median CONFiRM scores for each overall magnitude of response (step 3)

	Paediatric CONFiRM			Adult CONFiRM		
	All	HCPs	Patient advocates	All	HCPs	Patient advocates
	Median (25^{th},75^{th} %)	Median (25^{th},75^{th} %)	Median (25^{th},75^{th} %)	Median (25^{th},75^{th} %)	Median (25^{th},75^{th} %)	Median (25^{th},75^{th} %)
Deleterious	-14 (-18, -9)	-14 (-18, -10)	-14 (-18, -9)	-23 (-23, -14)	-23 (-23, -19)	-21 (-23, -3)
Non-response	-12 (-12, 2)	-12 (-12, 4)	-7 (-7, 12)	14 (7, 15)	14 (4, 15)	8 (4, 14)
Sufficient	17 (11, 17)	17 (14, 31)	11 (-12, 17)	18 (14, 19)	14 (14, 19)	19 (14, 22)
Substantial	33 (31, 34)	33 (31, 34)	34 (31, 36)	30 (28, 31)	30 (28, 31)	30 (28, 31)
Super-response	39 (36, 51)	39 (36, 52)	37 (35, 53)	37 (35, 43)	38 (25, 43)	37 (35, 43)

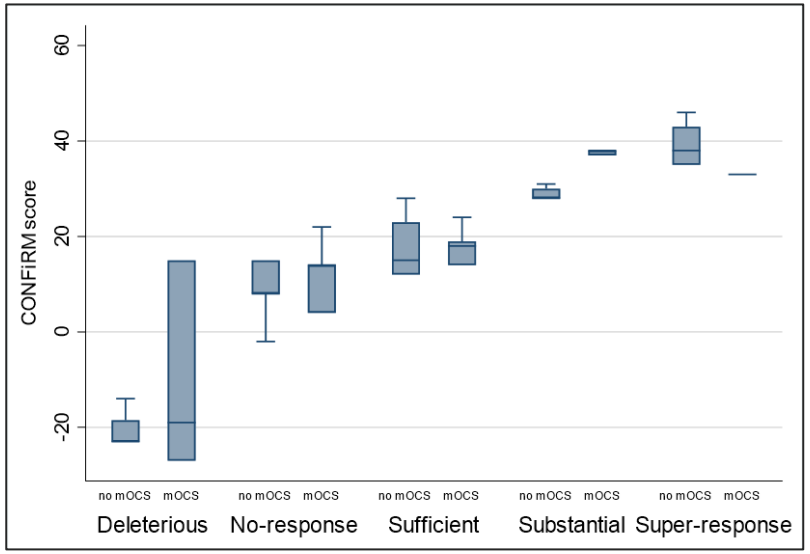
CONFiRM, CompOsite iNdex For Response in asthMa; HCPs, healthcare professionals.

Figure S4. Sensitivity analysis for patient profiles depending on taking maintenance oral corticosteroids at baseline (step 3)

A. Paediatric CONFiRM



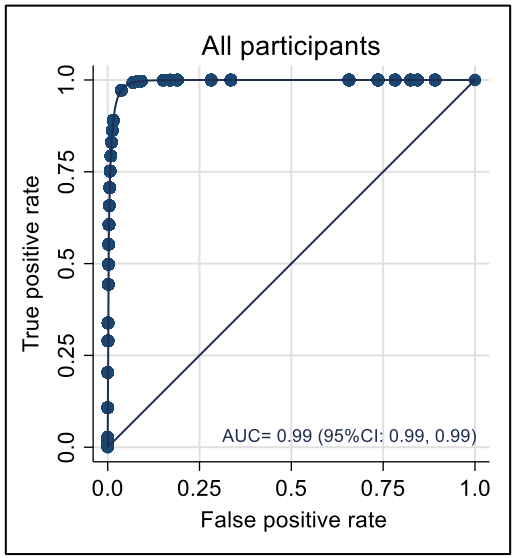
B. Adult CONFiRM Response

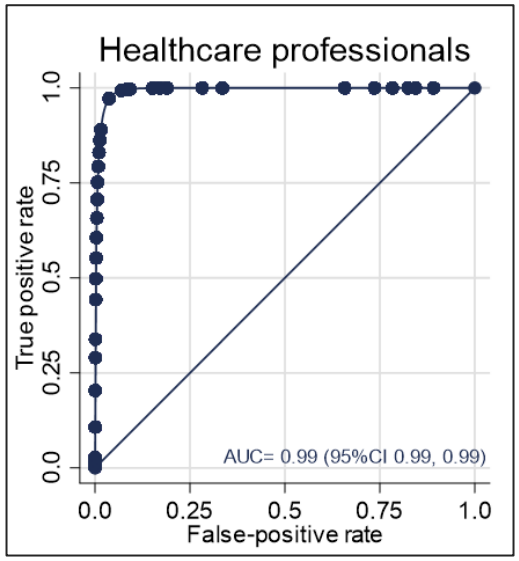


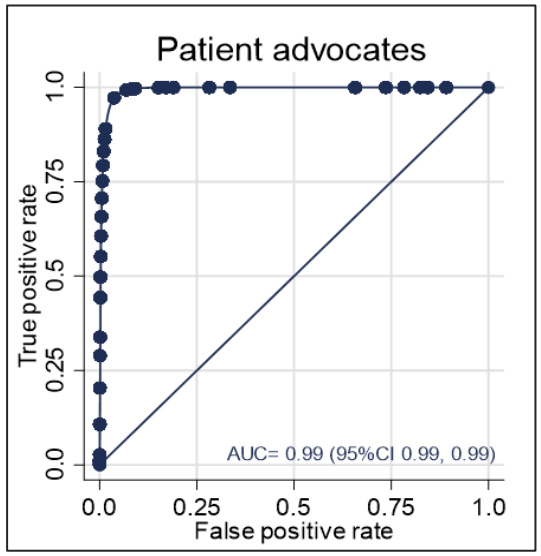
Box and whisker plot show the 1000minds score for patient profile with each magnitude of overall response by OCS treatment at baseline. Response (deleterious to super-response) was the most frequent (modal) response by all participants for each of the 50 patient profiles. Total composite score for these patients was calculated based on relative weights for each outcome measure assigned at step 2 (1000minds). CONFiRM score for each patient profile case represented by box and whisker plots (box: median with 25^{th} and 75^{th} centiles; lines represent 2.5 to 97.5 centiles). Weighting of each patient profile in the dataset was calculated based on the number of patient cases per cluster. Maintenance oral corticosteroid use is defined as daily or alternate day use of oral corticosteroids for asthma. CONFiRM, CompOsite iNdex For Response in asthMa.

Figure S5. Receiver operator curves for substantial response compared with less than substantial response (step 3)

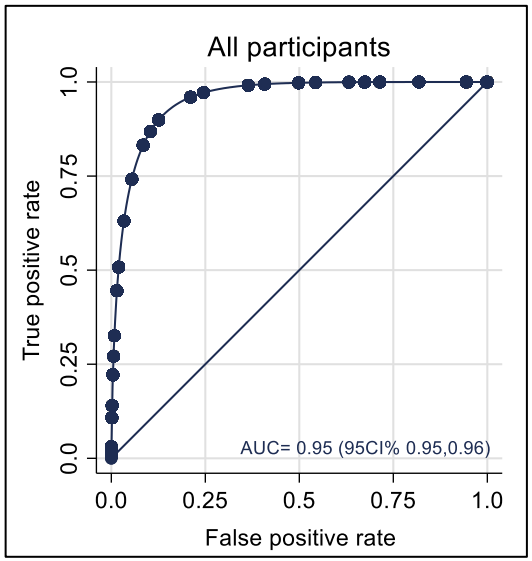
A. Paediatric CONFiRM

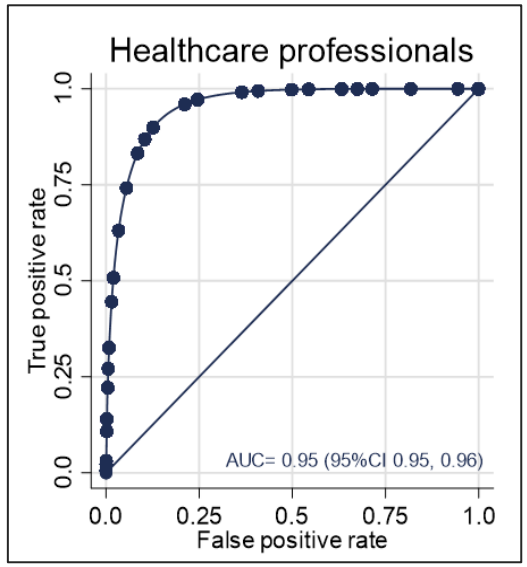


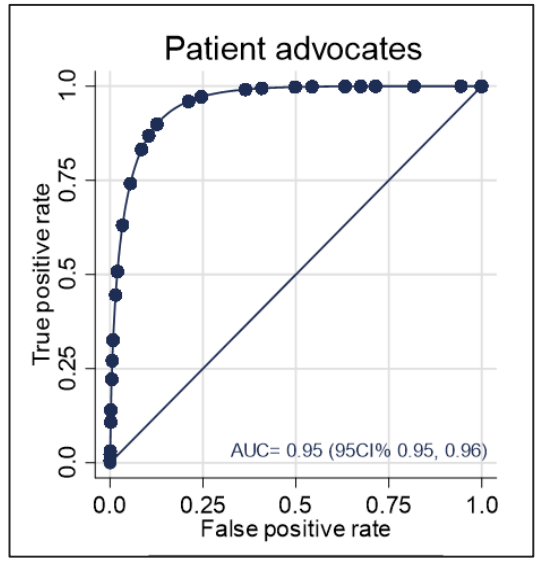




B. Adult CONFiRM



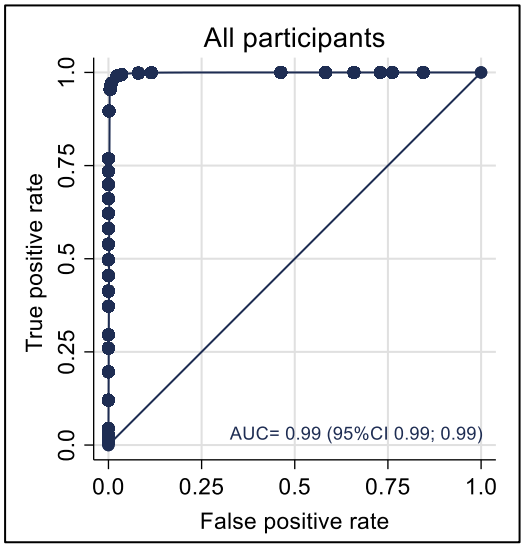


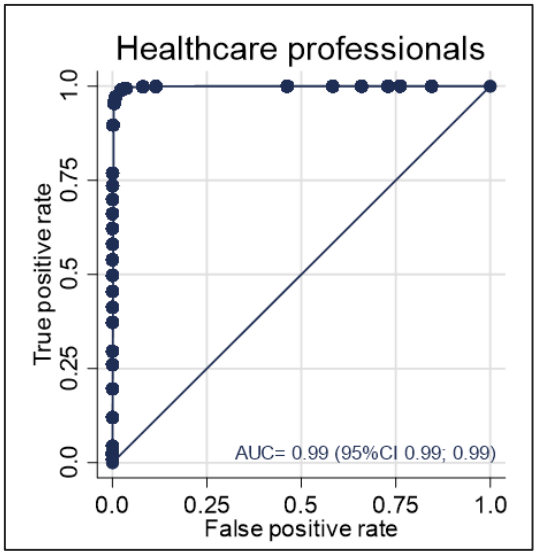


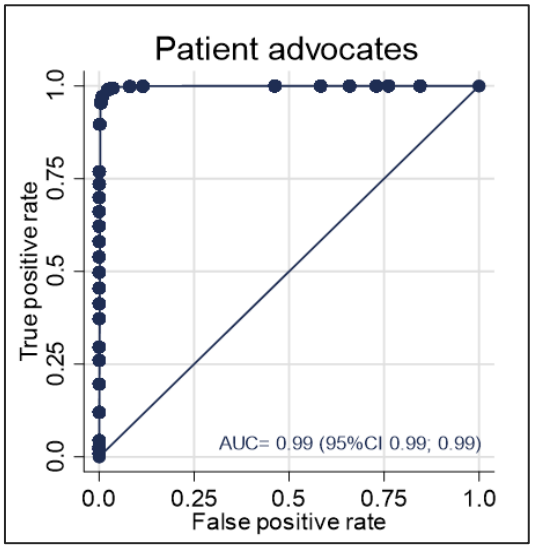
Gold standard taken from participants' rating of response for 50 patient profiles. Compared to CONFiRM score for each patient case. Substantial response is ''an improvement in asthma that a patient would consider as being 'big enough' to justify the use of biological therapy for their asthma (Box 1). It is expected that a substantial response would be larger than sufficient response but smaller than super-response''. Weighting of each patient profile in the dataset was calculated based on the number of patient profiles per cluster. AUC: area under the curve; CONFiRM, CompOsite iNdex For Response in asthMa.

Figure S6. Receiver operator curves for sufficient response compared with less than sufficient response. (step 3)

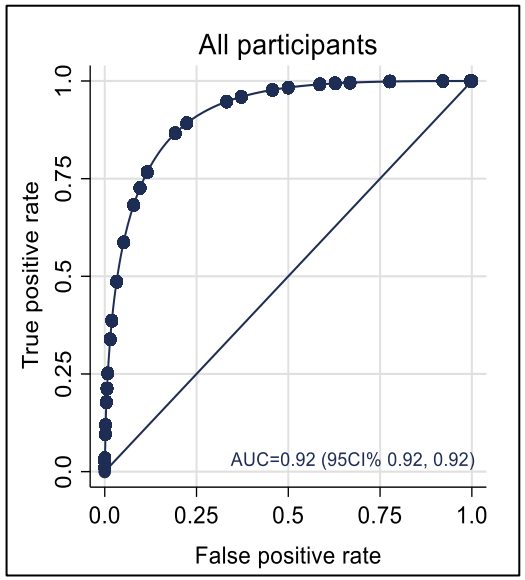
A. Paediatric CONFiRM

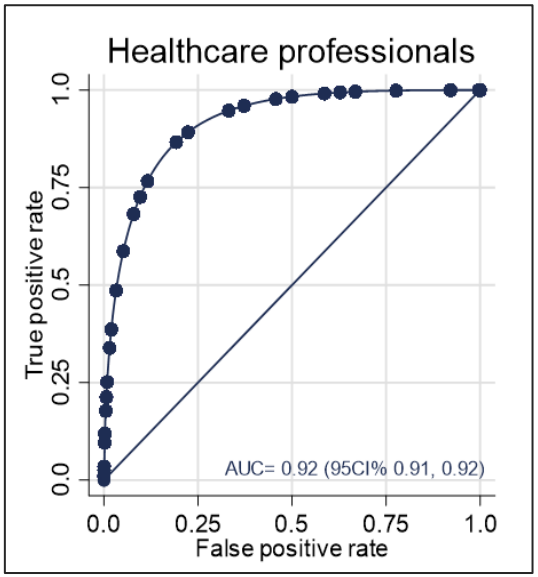


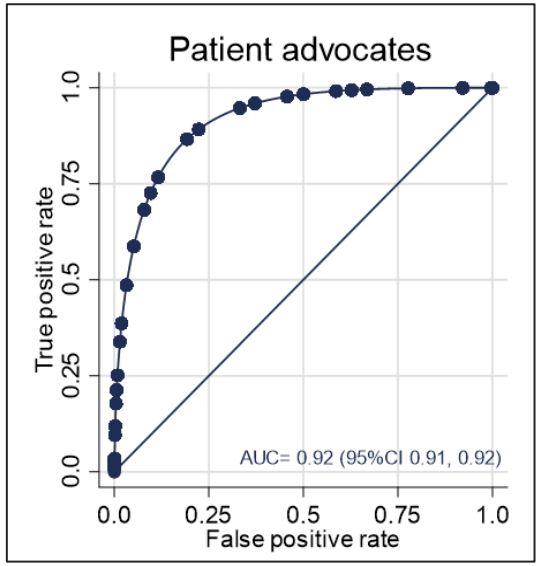




B. Adult CONFiRM







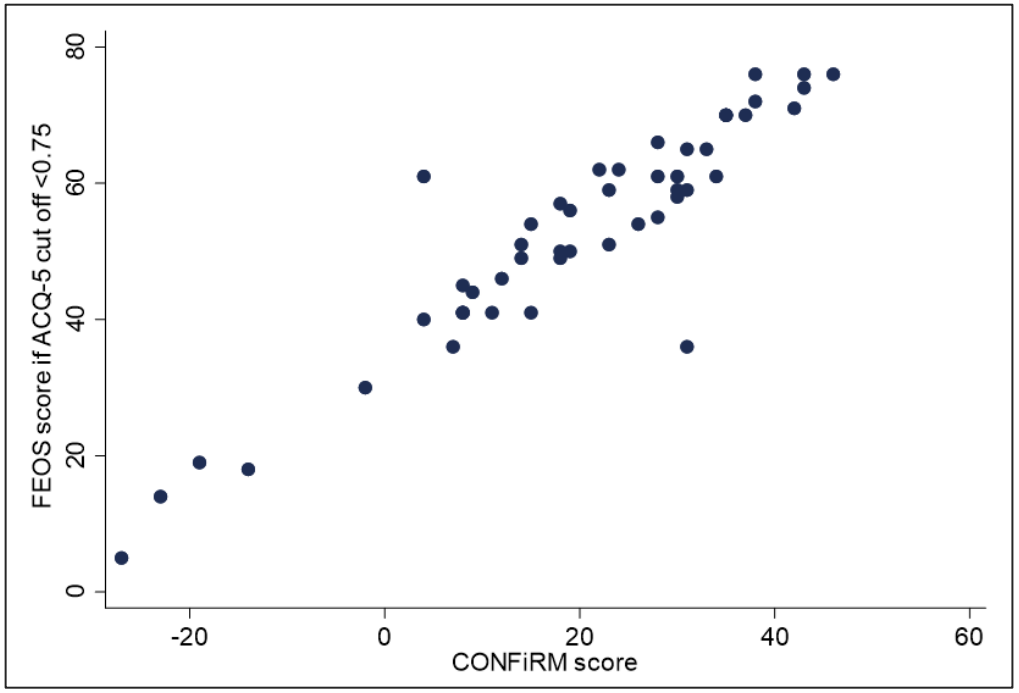
Gold standard taken from participants' rating of response for 50 patient profiles. Compared to CONFiRM score for each patient case. Sufficient response is ''the smallest improvement in asthma that a patient would consider as important and would help in further doctor-patient decision-making (Box 1)''. Weighting of each patient profile in the dataset was calculated based on the number of patients per cluster. AUC: area under the curve; CONFiRM, CompOsite iNdex For Response in asthMa.

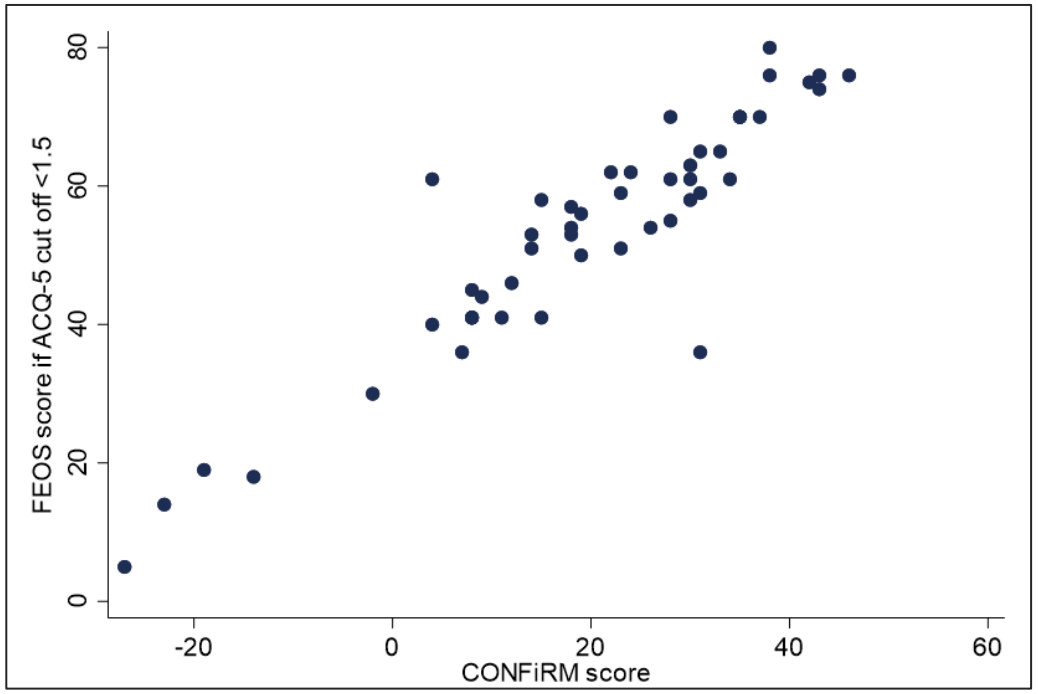
Table S16. Receiver operator curves analysis using bootstrap approach. (step 3)

	Sufficient and less than sufficient response AUC (95%CI)				Substantial and less than substantial response AUC (95%CI)			
	Paediatric CONFiRM		Adult CONFiRM		Paediatric CONFiRM		Adult CONFiRM	
	non-bootstrap AUC	bootstrap AUC	non-bootstrap AUC	bootstrap AUC	non-bootstrap AUC	bootstrap AUC	non-bootstrap AUC	bootstrap AUC
All participants	0.99 (0.99; 0.99)	0.99 (0.99; 0.99)	0.92 (0.92,0.92)	0.96 (0.95, 0.96)	0.99 (0.99, 0.99)	NA	0.95 (0.95,0.96)	0.95 (0.94, 0.95)
Not on mOCS at baseline	0.99 (0.99; 0.99)	0.99 (0.98; 0.99)	0.96 (0.95,0.96)	0.97 (0.96, 0.98)	NA	NA	0.94 (0.93, 0.95)	0.93 (0.92, 0.94)
On mOCS at baseline	NA	NA	0.83 (0.82, 0.84)	0.96 (0.95, 0.97)	NA	NA	0.99 (0.99, 0.99)	NA
HCPs	0.99 (0.99; 0.99)	0.99 (0.99; 0.99)	0.92 (0.91,0.92)	0.96 (0.95, 0.97)	0.99 (0.99, 0.99)	NA	0.95 (0.95, 0.96)	0.95 (0.94, 0.96)
Not on mOCS at baseline	0.99 (0.99; 0.99)	0.99 (0.98; 0.99)	0.96 (0.95, 0.97)	0.97 (0.96, 0.98)	NA	NA	0.94 (0.93, 0.95)	0.93 (0.92, 0.95)
On mOCS at baseline	NA	NA	0.83 (0.82, 0.84)	0.96 (0.95, 0.97)	NA	NA	0.99 (0.99, 0.99)	NA
Patient advocates	0.99 (0.99; 0.99)	0.99 (0.99; 0.99)	0.92 (0.91, 0.92)	0.96 (0.95, 0.97)	0.99 (0.99, 0.99)	NA	0.95 (0.95, 0.96)	0.95 (0.94, 0.96)
Not on mOCS at baseline	0.99 (0.99; 0.99)	0.99 (0.98; 0.99)	0.96 (0.95, 0.97)	0.97 (0.96, 0.98)	NA	NA	0.94 (0.93, 0.95)	0.93 (0.92, 0.95)
On mOCS at baseline	NA	NA	0.83 (0.82,0.85)	0.96 (0.95, 0.97)	NA	NA	0.99 (0.99, 0.99)	NA

AUC, area ander the curve; CONFiRM, CompOsite iNdex For Response in asthMa; HCPs, healthcare professionals; NA, not avaliable because AUC not calcuable as data either perfectly predicts outcome or zero participants in one cell; mOCS, maintenance oral corticosteroids.

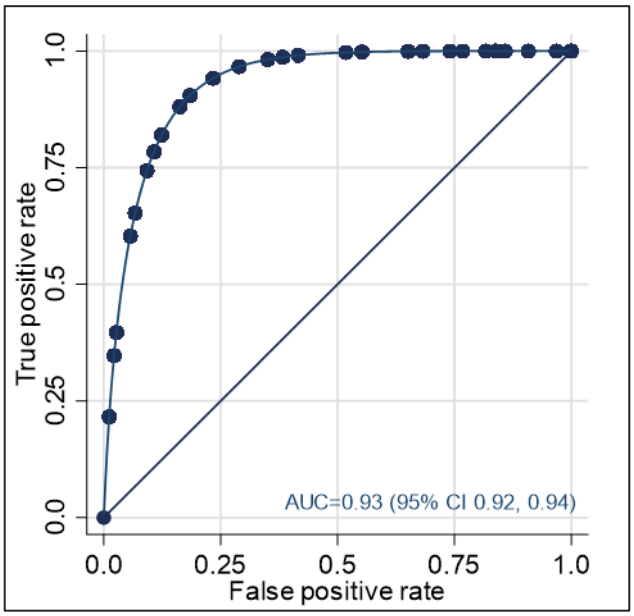
Figure S7. Validation of the adult CONFiRM against FEOS composite score (step 3).





As FEOS[5] has asthma control test (ACT), we converted the levels of ACT into ACQ-5 with different levels of cut-offs (1.5 and 0.75). We then calculated the total score for patient profiles for these two composite definitions of response tools. Intraclass correlation coefficient (absolute-agreement, 2-way mixed-effects model) for 0.75 and 1.5 ACQ-5 cut offs were very high ((r=0.93 (0.88 to 0.96) and r=0.92 (95%CI 0.87 to 0.96) respectively). ACQ: Asthma Control Questionnaire; CONFiRM: CompOsite iNdex For Response in asthMa; FEOS: FEV1, Exacerbations, Oral Corticosteroids, Symptoms Score.

Figure S8. Receiver Operator Curve for adult CONFiRM to identify super-responders as per the super-responder Delphi definition. (step 3)



Gold standard taken from participants' rating of super-response for 50 patient profiles and compared to super-responders identified based on super-responder Delphi definition[15]. AUC: area under the curve. Bootlegged AUC is 0.88 (95%CI 0.86 to 0.90). Weighting of each patient profile in the dataset was calculated based on the number of patients per cluster. CONFiRM: CompOsite iNdex For Response in asthMa.

Table S17. Changes implemented after stakeholder meetings.

Changes proposed by the stakeholder groups
Additional sensitivity analysis for patient profiles on and not on maintenance oral corticosteroids for asthma at baseline
Include weighted cases according to frequency of the patient profiles in the dataset
Report modal response
Rescale the composite from 0 to 100 into – 31 to 69
Utilise bootstrapping approach for calculating AUCs to check for overfitting

AUC, area under the curve.

Appendix 12. Step 4 results: External validation

Table S18 describes the 15 new cases paediatric and adult profiles that were selected for the external validation**. Table S19** describes the new group of 97 participants from 28 countries who took part in assessing overall magnitude of response for these profiles**. Table S20** summarises the ICCs for the particants' responses for repeated the profiles. These were 0.59 and 0.65 for paediatric and 0.12 and 0.70 for adult profiles.

Figure 5 and **Table S21** summarise the relationship between the CONFiRMs score for each patient profile and overall magnitude of change. Similar results were found for adult patient profiles where mOCS was not used at baseline **(Figure S9).**

Figure S10 describes the composite measures ability to discriminative between substantial response as compared with less than substantial response. This was excellent for both the paediatric (AUC= 0.99, 95% CI 0.99, 1.0) and adult (0.98, 0.97; 0.98) CONFiRM scores. This was also seen for sufficient response as compared with less than sufficient response (paediatric 0.99 (95% CI 0.99, 1.0); adult 0.98 (95% CI 0.98, 0.98)) **(Figure S10).**

Table S18. Description of patient profiles from step 4.

	Paediatric profiles (n=15)		Adult profiles (n=15)	
	Baseline	1 year follow up	Baseline	1 year follow up
Age, median (IQR)	13.0 (10.0; 15.0)		47.0 (33.0; 53.0)	
Gender Female, n (%)	5 (33.3)		6 (40.0)	
Biological therapy, n (%) Dupilumab Benralizumab Mepolizumab Omalizumab	0 (0.0) 0 (0.0) 2 (13.3) 13 (86.7)		2 (13.3) 1 (6.7) 3 (20.0) 9 (60.0)	
Severe asthma exacerbations, median (IQR)	10.0 (7.0; 10.0)	5.0 (1.0; 9.0)	4.0 (3.0; 5.0)	2.0 (0.0; 4.0)
Maintenance OCS, n (%)	0 (0.0)	2.0 (13.3)	5.0 (33.3)	4.0 (26.6)
Maintenance OCS dose, mg (IQR)	0 (0.0)	NA	5.0 (5.0; 22.5)	13 (6.8; 22.5)
On treatment FEV_1, median (IQR) %	78.0 (64.0; 87.0)	83.0(65.0; 100.0)	64.9 (51.0; 75.0)	71.6 (54.4; 84.0)
SAQ, median (IQR), points	NA	NA	3.8 (3.5; 4.1)	4.1 (3.6; 4.6)
PAQLQ, median (IQR), points	5.3 (3.4; 5.7)	6.2 (4.0; 6.4)	NA	NA
C-ACT/ ACT, median (IQR), points	15.0 (10.0;17.0)	20.0 (13.0; 22.0)	NA	NA
ACQ-5, median (IQR), points			3.6 (2.8; 4.0)	1.0 (0.4; 3.4)

Overall magnitude of change*, n (%)				
Deleterious	-	3 (20)	-	3 (20)
No change	-	5 (33)	-	3 (20)
Sufficient response	-	1 (7)	-	3 (20)
Substantial response	-	3 (20)	-	3 (20)
Super-response	-	3 (20)	-	3 (20)

Table summarises the description of patient profiles used in the step 4. *Overall magnitude of change (box 1) according to rating of HCPs and patient advocates. Severe asthma exacerbations are defined as per ATS/ERS guideline.[23] Maintenance oral corticosteroid use is defined as daily or alternate day use of oral corticosteroids. ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Test; COMSA, Core Outcome Measures sets for paediatric and adult severe asthma; IOR, interquartile range; FEV_1, percent predicted forced expiratory volume in 1 second; NA, not applicable; NI no information; OCS, oral corticosteroids; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; SAQ, Severe Asthma Questionnaire.

Table S19. Overall demographic information about survey respondents in step 4.

	Paediatric profiles n (%) n=44	Adult profiles n (%) n=53
Country		
United Kingdom	3 (6.8)	13 (24.5)
Italy	7 (15.9)	4 (7.6)
France	3 (6.8)	6 (11.3)
Greece	3 (6.8)	4 (7.6)
Germany	4 (9.1)	3 (5.7)
Malta	5 (11.4)	0 (0.0)
Austria	3 (6.8)	2 (3.8)
United States	2 (4.5)	3 (5.7)
Sweden	2 (4.5)	2 (3.8)
Canada	2 (4.5)	2 (3.8)
Belgium	3 (6.8)	1 (1.9)
Spain	1 (2.3)	1 (1.9)
Singapore	0 (0.0)	2 (3.8)
Slovakia	1 (2.3)	1 (1.9)
Australia	0 (0.0)	1 (1.9)
Croatia	1 (2.3)	0 (0.0)
Ireland	1 (2.3)	0 (0.0)
Romania	1 (2.3)	0 (0.0)
Serbia	1 (2.3)	0 (0.0)
Netherlands	1 (2.3)	0 (0.0)
Czech Republic	0 (0.0)	1 (1.9)
Denmark	0 (0.0)	1 (1.9)
Finland	0 (0.0)	1 (1.9)
Iceland	0 (0.0)	1 (1.9)
Poland	0 (0.0)	1 (1.9)
Portugal	0 (0.0)	1 (1.9)
South Korea	0 (0.0)	1 (1.9)
Switzerland	0 (0.0)	1 (1.9)
Gender		
Male	20 (45.4)	31 (58.5)
Female	24 (54.6)	22 (41.5)
Age group, years		

26-36		3 (5.7)
37-47	13 (29.6)	19 (35.9)
48-58	17 (38.6)	20 (37.8)
59-69	14 (31.8)	10 (18.9)
70-80	0 (0.0)	1 (1.9)
Duration of treating patients with severe asthma		
0-5 years	1 (2.3)	3 (5.7)
5-10 years	21 (47.7)	16 (30.2)
10-20 years	5 (11.4)	18 (34.0)
Over 20 years	17 (38.6)	16 (30.2)
Part of an advisory board, national/international severe asthma working group in the past 5 years		
Yes	32 (72.7)	47 (88.7)
No	12 (27.3)	6 (11.3)
Author of a severe asthma and biological therapies publication in the past 5 years		
Yes	28 (63.6)	44 (83.0)
No	16 (36.4)	9 (17.0)
Practice setting		
Academic hospital/clinic	40 (90.9)	49 (92.5)
Non-academic hospital/clinic	4 (9.1)	4 (7.5)
Work in a specialist severe asthma unit		
Yes	38 (86.4)	50 (94.3)
No	5 (11.4)	3 (5.7)
Not applicable	1 (2.3)	0 (0.0)
Number of patients with severe asthma on biological therapy per year under your care		
<5	7 (15.9)	0 (0.0)
5-10	8 (18.2)	1 (1.9)
11-20	13 (29.6)	6 (11.3)
21-50	10 (22.7)	10 (18.9)
51-100	4 (9.0)	6 (11.3)
101-200	2 (4.6)	12 (22.6)
>201	0 (0.0)	18 (34.0)
Speciality**		
Pulmonologist	41 (77.4)	0 (0.0)
Paediatrician	0 (0.0)	15 (34.1)
Allergist + Pulmonologist + Paediatrician	0 (0.0)	9 (20.5)
Pulmonologist+ Paediatrician	0 (0.0)	7 (15.9)
Allergist + Pulmonologist + Paediatrician+ Clinical researcher	0 (0.0)	6 (13.6)
Allergist	4 (7.6)	2 (4.6)
Allergist + Pulmonologist	4 (7.6)	0 (0.0)
Other	0 (0.0)	2 (4.6)
Pulmonologist +Clinical researcher	2 (3.8)	0 (0.0)
Allergist + Paediatrician	1 (1.9)	1 (2.3)
Pulmonologist + Other (please specify)	0 (0.0)	1 (2.3)
Pulmonologist+ Paediatrician +Clinical researcher	0 (0.0)	1 (2.3)
Allergist+ Clinical researcher	1 (1.9)	0 (0.0)
Looking after		
Adults with severe asthma only (≥ 18 years)	0 (0.0)	49 (92.5)
Paediatric patients with severe asthma only (6-17years)	42 (95.5)	0 (0.0)
Both adult and paediatric patients with severe asthma	2 (4.5)	4 (7.5)

Table S20. Intraclass correlation for repeated patient profiles in step 4

	Paediatric survey ICC (95%CI)		Adult survey ICC (95%CI)	
	Profiles P/C	Profiles Q/I	Profiles P/D	Profiles Q/K
All participants	0.66 (0.37 to 0.81)	0.59 (0.24 to 0.78)	0.12 (-0.57 to 0.50)	0.70 (0.47 to 0.83)

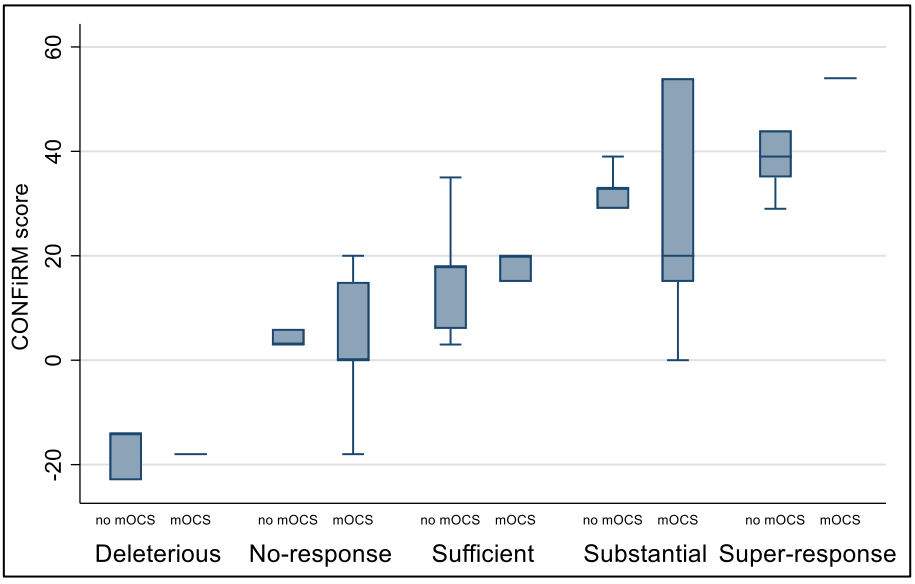
Intraclass correlation coefficient[14] (ICC) estimates and their 95% confident intervals were calculated using STATA software version 16.1 based on an absolute-agreement, 2-way mixed-effects model. ICC was used to calculate agreement between responses from HCP for the repeated patient profiles. Values less than 0.5 are indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.90 indicate excellent reliability.

Table S21. Median CONFiRM scores for each overall magnitude of response (step 4)

	Paediatric CONFiRM	Adult CONFIRM
	Median (25^{th},75^{th} %)	Median (25^{th},75^{th} %)
Deleterious	-14 (-18;-14)	-18 (-23;-18)
Non-response	3 (-1;11)	3 (0;15)
Sufficient	33 (11;36)	18 (13;20)
Substantial	39 (36;42)	33 (29; 35)
Super-response	46 (39;46)	44 (39; 54)

CONFiRM, CompOsite iNdex For Response in asthMa.

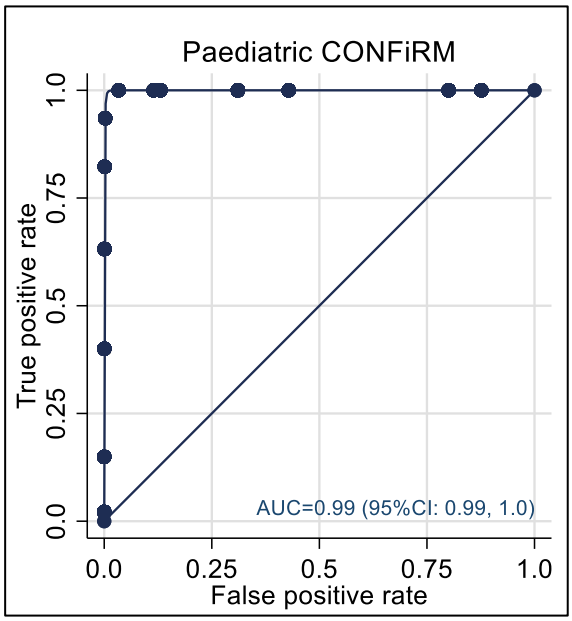
Figure S9. Sensitivity analysis for adult patient profiles depending on taking maintenance oral corticosteroids at baseline (step 4)

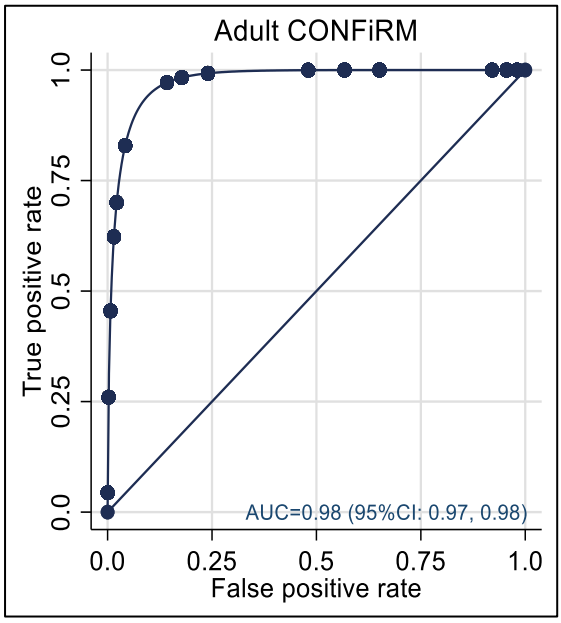


Box and whisker plot show the 1000minds score for patient profile with each magnitude of overall response by OCS treatment at baseline. Response (deleterious to super-response) was the most frequent (modal) response by all participants for each of the 15 patient profiles in the step 4. Total composite score for these patients was calculated based on relative weights for each outcome measure assigned at step 2 (1000minds). CONFiRM score for each patient profile case represented by box and whisker plots (box: median with 25th and 75th centiles; lines represent 2.5 to 97.5 centiles). Weighting of each patient profile in the dataset was calculated based on the number of patient cases per cluster. Maintenance oral corticosteroid use is defined as daily or alternate day use of oral corticosteroids for asthma. CONFiRM, CompOsite iNdex For Response in asthMa.

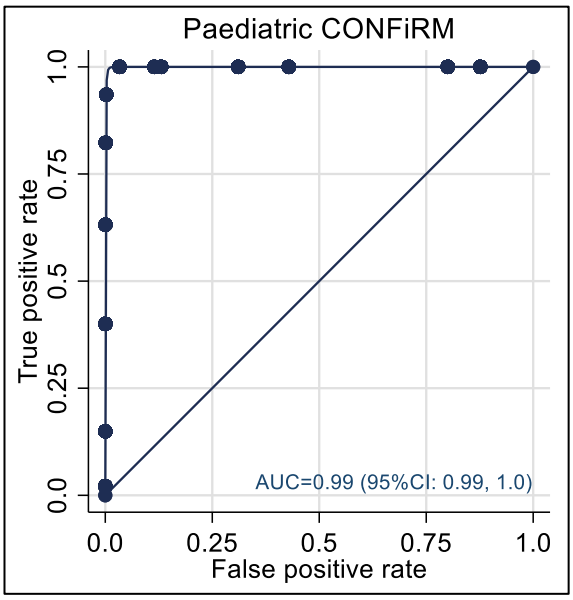
Figure S10. Receiver operator curves (ROC) for substantial and sufficient responses. (step 4)

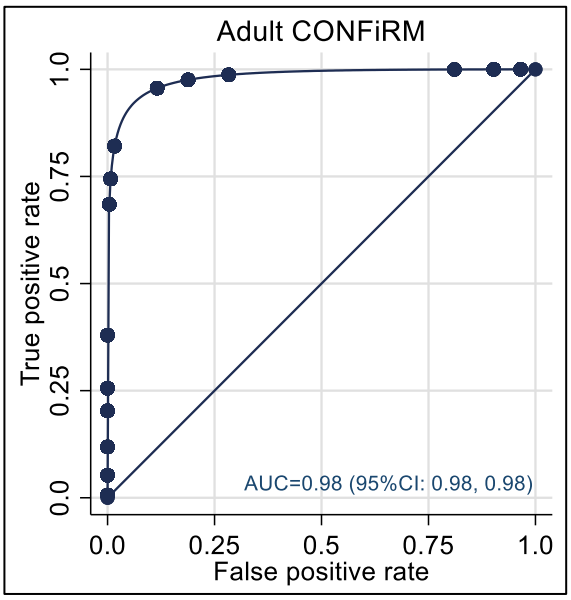
A. ROC for substantial response compared with less than substantial response.





B. ROC for sufficient response compared with less than sufficient response.





Gold standard taken from participants' rating of response for 15 patient profiles. Compared to CONFiRM score for each patient case. Sufficient response is ''the smallest improvement in asthma that a patient would consider as important and would help in further doctor-patient decision-making'' (Box 1). Substantial response is ''an improvement in asthma that a patient would consider as being 'big enough' to justify the use of biological therapy for their asthma. It is expected that a substantial response would be larger than sufficient response but smaller than super-response.'' Weighting of each patient profile in the dataset was calculated based on the number of patient profiles per cluster. AUC: area under the curve; CONFiRM, CompOsite iNdex For Response in asthMa; ROC: Receiver operator curve.

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