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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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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.

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 ($AUC \geq 0.92$) and a substantial ($AUC \geq 0.95$) 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.

BACKGROUND

Severe asthma affects up to 10% of adults and 2.5% of children with asthma¹ 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 burdensome³ and expensive^{4,5}. Hence, they should only be continued if a patient has an adequate response. Patients recognise that not all responses are meaningful³, however there is no agreed definition of either non-response or adequate response⁶. An expert task force of clinicians has proposed that patients should be classified as non-responders, intermediate responders and super-responders⁷ 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.

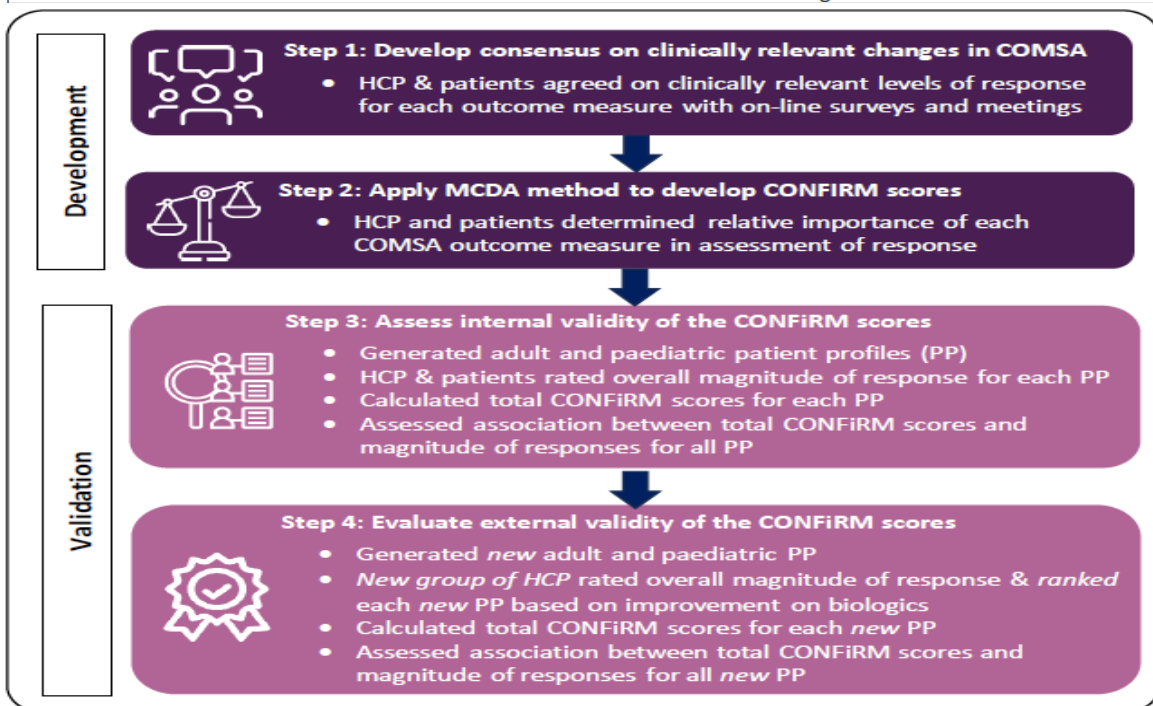
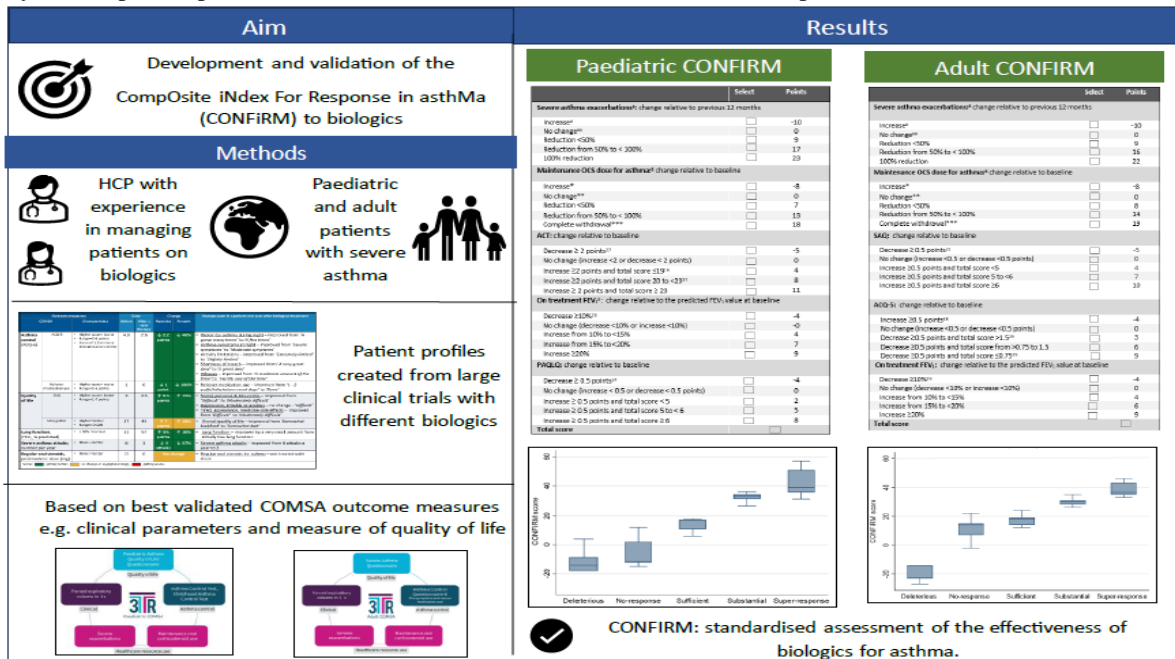
To standardise assessment, we have recently developed the Core Outcome Measures sets for paediatric and adult Severe Asthma (COMSA)¹² selected by four stakeholder groups: healthcare professionals (HCPs), patient advocates, pharmaceutical representatives, and regulators. Briefly, both the adult and paediatric COMSA include forced expiratory volume in 1 second (FEV₁), frequency of severe asthma exacerbations¹³ 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 COMSA¹² 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 COMSA12; 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).

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.



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 statement²⁵. 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**).

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 scenarios. 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; FEV1, percent predicted forced expiratory volume in 1 second; SAQ, severe asthma questionnaire.

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

Maintenance OCS dose for asthma Complete withdrawal 👍👍👍	Maintenance OCS dose for asthma Reduction <50% 👍
SAQ Increase ≥ 0.5 points and total score <5 👎	SAQ Increase ≥ 0.5 and SAQ total score ≥ 6 👍👍👍
This patient	This patient

They are the same

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%	<ul style="list-style-type: none"> 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%	
Quality of life	SAQ	• Higher score= better • Range=1-7 points	3	3.5	↑ 0.5 points	↑ 15%	<ul style="list-style-type: none"> 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%	
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 Non-response Sufficient response Substantial response Super-response

Table 1. CompOSite iNdex For Response in asthMa (CONFIRM) in children and adults

A. Paediatric CONFIRM

Select	Points
Severe asthma exacerbations^a: change relative to previous 12 months	
Increase ^a	-10
No change ^{ab}	0
Reduction <50%	9
Reduction from 50% to < 100%	17
100% reduction	23
Maintenance OCS dose for asthma^a: change relative to baseline	
Increase ^a	-8
No change ^{ab}	0
Reduction <50%	7
Reduction from 50% to < 100%	13
Complete withdrawal ^{abc}	18
ACT: change relative to baseline	
Decrease ≥ 2 points ^{cd}	-5
No change (increase <2 or decrease < 2 points)	0
Increase ≥2 points and total score ≤19 ^{de}	4
Increase ≥2 points and total score 20 to <23 ^{de}	8
Increase ≥ 2 points and total score ≥ 23	11
On treatment FEV₁^f: change relative to the predicted FEV₁ value at baseline	
Decrease ≥10% ^{gh}	-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 ^{ij}	-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^a: change relative to previous 12 months	
Increase ^a	-10
No change ^{ab}	0
Reduction <50%	9
Reduction from 50% to < 100%	16
100% reduction	22
Maintenance OCS dose for asthma^a: change relative to baseline	
Increase ^a	-8
No change ^{ab}	0
Reduction <50%	8
Reduction from 50% to < 100%	14
Complete withdrawal ^{abc}	19
SAQ: change relative to baseline	
Decrease ≥ 0.5 points ^{cd}	-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 ^{gh}	-4
No change (increase <0.5 or decrease <0.5 points)	0
Decrease ≥0.5 points and total score >1.5 ^{de}	3
Decrease ≥0.5 points and total score from >0.75 to 1.5	6
Decrease ≥0.5 points and total score ≤0.75 ^{de}	9
On treatment FEV₁^f: change relative to the predicted FEV₁ value at baseline	
Decrease ≥10% ^{gh}	-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 CONFIRM 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 FEV1 is calculated as [(follow up FEV1 minus baseline FEV1 divided by predicted FEV1 value) x 100].²⁶ Percent predicted FEV1 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; FEV1, forced expiratory volume in 1 second; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; OCS, oral corticosteroids; SAQ, Severe Asthma Questionnaire.

Step 3: Assess internal validity of CONFIRM scores

Generating paediatric and adult patient profiles

Anonymised patient profiles were selected from 2011 patients³⁰⁻³⁶ 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**).

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**).

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 (FEV1, exacerbations, OCS, symptoms)⁸ and a ROC analysis for comparison with the super-response definition⁹.

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

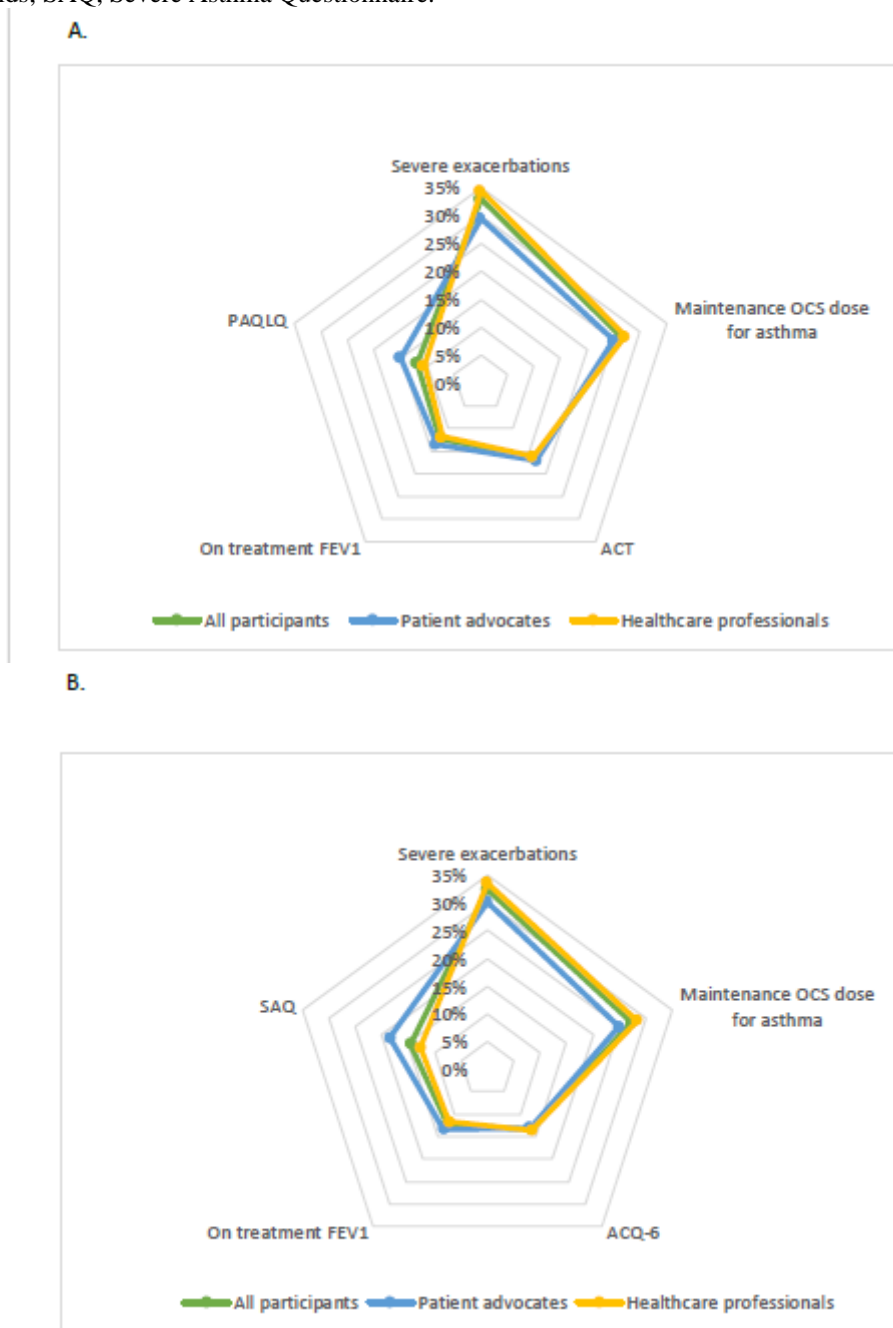
Step 1: Develop consensus levels of clinically relevant changes for each COMSA outcome measure

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**.

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 COMSA12 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; FEV1, percent predicted forced expiratory volume in 1 second; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; OCS, oral corticosteroids; SAQ, Severe Asthma Questionnaire.



Step 3: Assess internal validity of CONFIRM scores

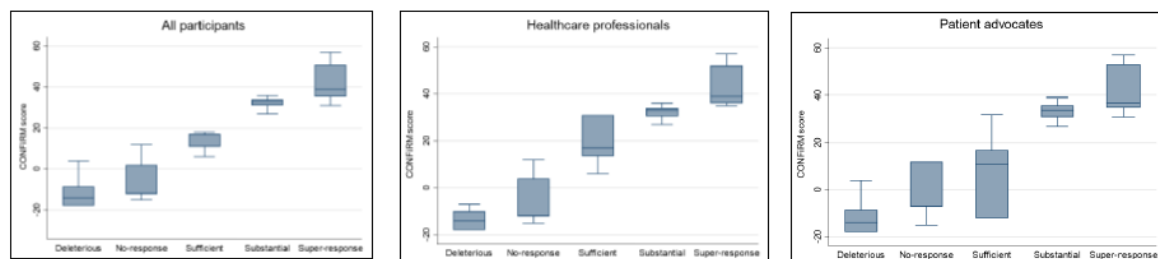
The patient profiles used in this step are summarised in **Table S12**. A total of 146 participants took part: 79 [45 (57.0%) HCPs; 34 (43.0%) patient advocates] reviewed the adult profiles and 67 [44 (65.7%) HCP; 23 (34.3%) patient advocates] reviewed the paediatric profiles. (**Table S13**). Patient 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.

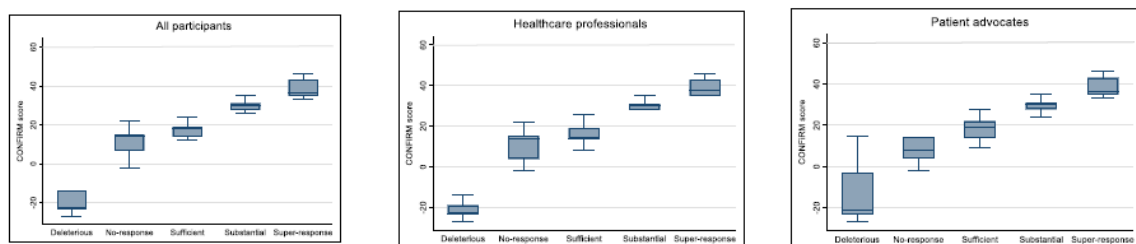
There was a clear relationship between the CONFIRM scores for each patient profile and participants' rating of overall magnitude of response (**Figure 4, Table S15**). Similar results were found for patient profiles where mOCS was not used at baseline (**Figure S4**).

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 $\chi^2= 2623.1$, $p<0.0001$; $\chi^2=2506.5$, $p<0.0001$; $\chi^2= 2657.1$, $p<0.0001$ for all participants, patient advocates and HCPs respectively) and adult CONFIRMs ($\chi^2= 2974.7$, $p<0.0001$; $\chi^2= 2854.3$, $p<0.0001$; $\chi^2= 3216.3$, $p<0.0001$). CONFIRM, CompOSite iNdex For Response in asthMa.

A. Paediatric CONFIRM



B. Adult CONFIRM



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 FEOS8 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 definition9 (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**).

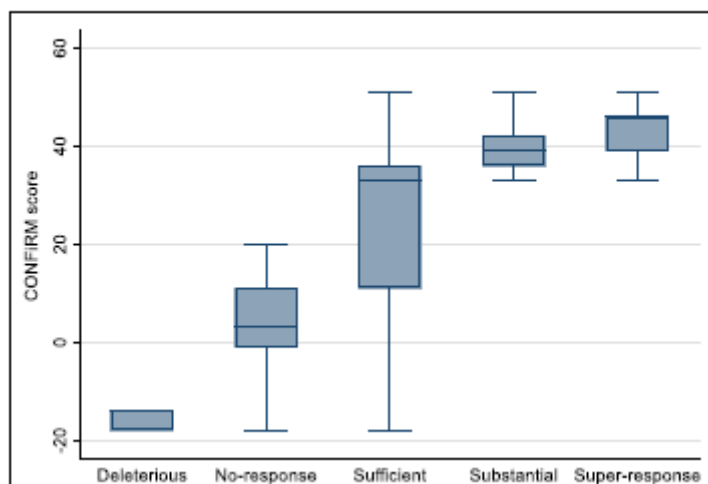
Step 4. Assess external validity of the CONFIRM scores

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**).

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 $\chi^2= 502.7$, $p<0.0001$) and adult CONFIRM tools ($\chi^2= 648.5$, $p<0.0001$). CONFIRM, CompOsite iNdex For Response in asthMa. Similar results were found for adult patient profiles where mOCS was not used at baseline (**Figure S11**).

A. Paediatric CONFIRM



B. Adult CONFIRM

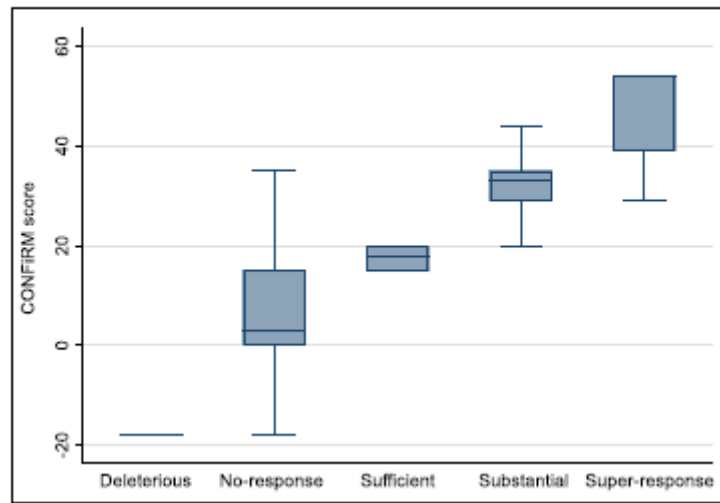
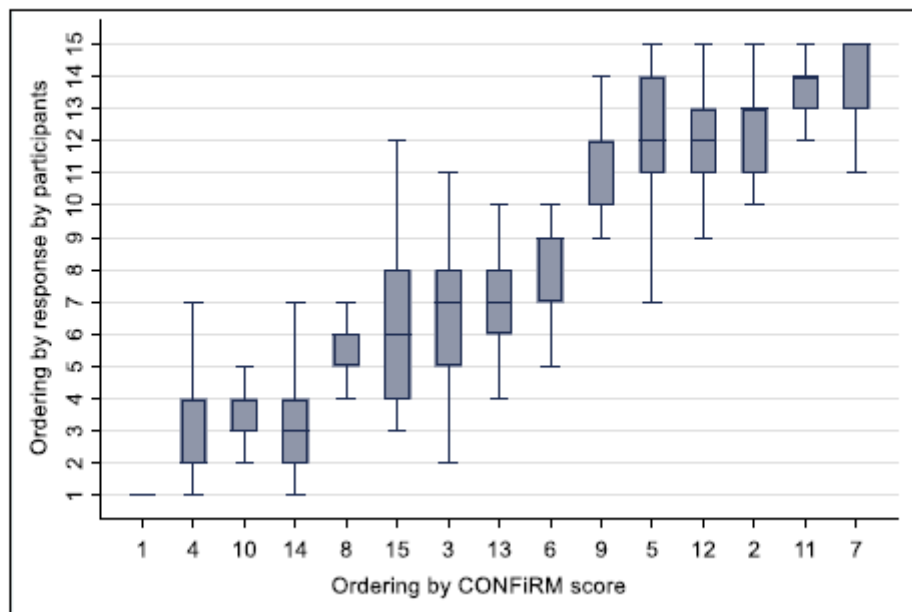
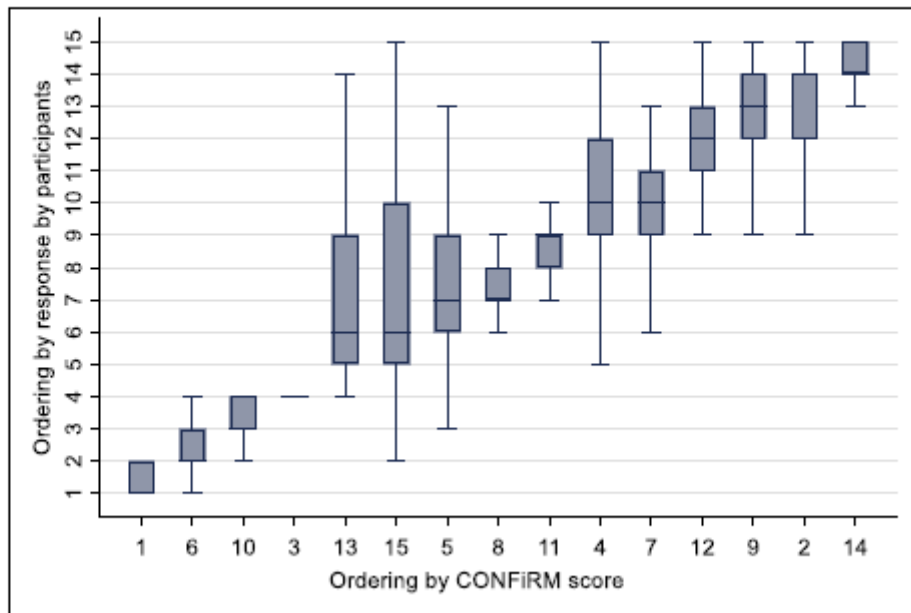


Figure 6. Ranking of the 15 patient profiles in order of improvement on biologics from 1st (worsening) to 15th (largest improvement) in stage 4. A. Paediatric patient profiles. B. Adult patient profiles. Ranks for each patient profile are represented by box and whisker plots (box: median with 25th and 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 ($p<0.0001$))

A. Paediatric survey.



B. Adult survey.



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 COMSA12 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 FEOS8 and the super-responder⁹ 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. FEOS8 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 FEV1 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

Ekaterina Khaleva declares funding from 3TR European Union Innovative Medicines Initiative 2 and Asthma, Allergy & Inflammation Research (AAIR) Charity to her institution. Chris Brightling declares grants and consulting fees from GSK, AZ, Sanofi, Regeneron, Roche, Genentech, Novartis, Chiesi, Mologic paid to institution; and support from the 3TR project and NIHR BRC.

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