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Development of patient-centred outcomes in asthma and allergy

by

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Thesis for the degree of Doctor of Philosophy in Medicine by Published Work

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Abstract

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Asthma and allergies are associated with significantly reduced quality of life and both morbidity and mortality. They affect patients from childhood into adulthood. Patients often miss school, college or work. To improve outcomes for these patients we need to better understand what is important for them. This includes patient-oriented guidance, use of personalised medicines and being able to assess response to medicines using patient-selected outcomes.

This thesis focuses on developing patient-centred outcomes for patients with asthma and/or allergies and has four main aims. First, to understand perceptions of adolescents and young adults with allergies and/or asthma and their parents about transition care to improve outcomes. Second, to generate patient-centred core outcome measures sets for paediatric and adult severe asthma. Third, to systematically review and appraise methodologically developed, defined, and evidenced definitions of response to biological therapy as outcomes for severe asthma. Forth, to develop composite response tools as standardised outcomes with input of patients to assess response to biological therapy for severe asthma.

The results achieved with patient input reported in this thesis include 1) views of adolescents and young adults with asthma and allergies and their parents on how to improve draft recommendations about transition; 2) development of core outcome measures for paediatric and adult severe asthma through the multinational multistakeholder consensus; 3) current definitions of response to biological therapies that lack of a patient-centred composite outcome measure of response, and 4) externally validated composite definitions of response to biological therapy for paediatric and adult severe asthma.

This thesis concludes that involvement of patients in guideline development is crucial to make recommendations more patient-centred thus improve long-term outcomes in adolescents and young adults with asthma and allergies. Novel core outcome measures for severe asthma should lead to consistency in reporting and standardised comparison of patient-oriented outcomes in trials to guide policy-making and clinical care. Methodologically developed patient-centred composite scores should be helpful in holistic understanding of response to biologics in severe asthma but require further validation. Taken together, this thesis is a step towards in achieving standardised and patient-oriented outcomes is asthma and allergy.

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Research Thesis: Declaration of Authorship

Print name: Ekaterina Khaleva

Title of thesis: Development of patient-centred outcomes in allergy and asthma.

I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. Parts of this work have been published as:

   • Perceptions of adolescents and young adults with allergy and/or asthma and their parents on EAACI guideline recommendations about transitional care: A European survey. **Khaleva E**, Knibb R, DunnGalvin A, Vazquez-Ortiz M, Comberiati P, Alviani C, Garriga-Baraut T, Gowland MH, Gore C, Angier E, Blumchen K, Duca B, Hox V, Jensen B, Mortz CG, Pite H, Pfaar O, Santos AF, Sanchez-Garcia S, Timmermans F, Roberts G. *Allergy*. 2022 Apr;77(4):1094-1104.

   • Development of Core Outcome Measures sets for paediatric and adult Severe Asthma (COMSA). **Khaleva E,** Rattu A, Brightling C, Bush A, Bossios A, Bourdin A, Chung KF, Chaudhuri R, Coleman C, Dahlén SE, Djukanovic R, Deschildre A, Fleming L, Fowler SJ, Gupta A, Hamelmann E, Hashimoto S, Hedlin G, Koppelman GH, Melén E, Murray CS, Pilette C, Porsbjerg C, Pike KC, Rusconi F, Williams C, Ahrens B, Alter P, Anckers F, van den Berge M, Blumchen K, Brusselle G, Clarke GW, Cunoosamy D, Dahlén B, Dixey P, Exley A, Frey U, Gaillard EA, Giovannini-Chami L, Grigg J, Hartenstein D, Heaney LG, Karadag B, Kaul S, Kull

I, Licari A, Maitland-van der Zee AH, Mahler V, Schoos AM, Nagakumar P, Negus J, Nielsen H, Paton J, Pijnenburg M, Ramiconi V, Romagosa Vilarnau S, Principe S, Rutjes N, Saglani S, Seddon P, Singer F, Staudinger H, Turner S, Vijverberg S, Winders T, Yasinska V, Roberts G; COMSA Working Group in the 3TR Consortium. *Eur Respir J.* 2023 Apr 3;61(4):2200606.

- Definitions of non-response and response to biological therapy for severe asthma: a systematic review. **Khaleva E,** Rattu A, Brightling C, Bush A, Bourdin A, Bossios A, Chung KF, Chaudhuri R, Coleman C, Djukanovic R, Dahlén SE, Exley A, Fleming L, Fowler SJ, Gupta A, Hamelmann E, Koppelman GH, Melén E, Mahler V, Seddon P, Singer F, Porsbjerg C, Ramiconi V, Rusconi F, Yasinska V, Roberts G. *ERJ Open Res*. 2023 May 2;9(3):00444-2022.

- Patient-centred composite scores as tools for assesment of response to biological therapy for paediatric and adult severe asthma. **Khaleva E,** Brightling C, Eiwegger T, Altraja A, Bégin P, Blümchen K, Bossios A, Bourdin A, Ten B.A, Brusselle G, Bumbacea R, Bush A, Casale T, Clarke G, Chaudhuri R, Chung K.F, Coleman C, Corren J, Dahlén SE, Deschildre A, Djukanovic R, Eger K, Exley A, Fleming L, Fowler S, Gaillard E, Gappa M, Gupta A, Haitchi H.M, Hashimoto S, Heaney L, Hedlin G, Henderson M, Hua W, Jackson D, Karadag B, Katelaris C, Koh M, Kopp M, Koppelman G, Kull I, Kurukulaaratchy R, Lee J.H, Mahler V, Mäkelä M, Masoli M, Mathioudakis A, Mazon A, Melén E, Milger K, Moeller A, Murray C, Nagakumar, P, Nair P, Negus J, Nieto A, Papadopoulos N, Paton J, Pijnenburg M, Pike K, Porsbjerg C, Rattu A, Rupani H, Rusconi F, Rutjes N, Saglani S, Seddon P, Siddiqui S, Singer F, Tajiri T, Turner S, Upham J, Vijverberg S, Wark P, Wechsler M, Yasinska V, Roberts G on behalf of the 3TR asthma definition of response working group. *Eur Respir J.* 2024, Nov 21:2400691 in press

Signature: Date: 02/02/2025

Additional research outputs.

Other co-authored publications related to Doctor of Philosophy (PhD) thesis over the past 4 years are detailed in Table i. Most of them are referenced in the thesis.

Table i. Research contributions and outputs.

Publication	Contribution by doctoral candidate	Link to the PhD thesis
Linked to chapter 1: Introduction		
Spolidoro GCI, Lisik D, Nyassi S, Ioannidou A, Ali MM, Amera YT, Rovner G, **Khaleva E**, Venter C, van Ree R, Worm M, Vlieg-Boerstra B, Sheikh A, Muraro A, Roberts G, Nwaru BI. Prevalence of tree nut allergy in Europe: A systematic review and meta-analysis. *Allergy*. 2024 Feb;79(2):302-323.	• Took part in the discussion of the findings. • Provided feedback on the manuscript.	• Summarised the prevalence of food allergy across Europe which evidences the burden of allergy.
Spolidoro GCI, Ali MM, Amera YT, Nyassi S, Lisik D, Ioannidou A, Rovner G, **Khaleva E,** Venter C, van Ree R, Worm M, Vlieg-Boerstra B, Sheikh A, Muraro A, Roberts G, Nwaru BI. Prevalence estimates of eight big food allergies in Europe: Updated systematic review and meta-analysis. *Allergy*. 2023 Sep;78(9):2361-2417.	• Took part in the discussion of the findings. • Provided feedback on the manuscript.	• Summarised the prevalence of eight big food allergies across Europe which evidences the burden of allergy.

Additional research outputs.

Publication	Contribution by doctoral candidate	Link to the PhD thesis
Spolidoro GCI, Amera YT, Ali MM, Nyassi S, Lisik D, Ioannidou A, Rovner G, **Khaleva E,** Venter C, van Ree R, Worm M, Vlieg-Boerstra B, Sheikh A, Muraro A, Roberts G, Nwaru BI. Frequency of food allergy in Europe: An updated systematic review and meta-analysis. *Allergy*. 2023 Feb;78(2):351-368.	• Took part in the discussion of the findings. • Provided feedback on the manuscript.	• Summarised the frequency of food allergies across Europe which evidences the burden of allergy.
Lisik D, Ioannidou A, Spolidoro G, Ali M, Nyassi S, Amera Y, Rovner G, **Khaleva E,** Venter C, van Ree R, Worm M, Vlieg-Boerstra B, Sheikh A, Muraro A, Roberts G, Nwaru BI. Prevalence of sensitization to molecular food allergens in Europe: A systematic review. *Clin Transl Allergy.* 2022 Jul 6;12(7):e12175.	• Took part in the discussion of the findings. • Provided feedback on the manuscript.	• Summarised the prevalence of sensitization to molecular food allergens across Europe which evidences the burden of allergy.
Muraro A, de Silva D, Halken S, Worm M, **Khaleva E,** Arasi S, Dunn-Galvin A, Nwaru BI, De Jong NW, Rodríguez Del Río P, Turner PJ, Smith P, Begin P, Angier E, Arshad H, Ballmer-Weber B, Beyer K, Bindslev-Jensen C, Cianferoni A, Demoulin C, Deschildre A, Ebisawa M, Fernandez-Rivas MM, Fiocchi A, Flokstra-de Blok B, Gerdts J, Gradman J, Grimshaw K, Jones C, Lau S, Loh R, Alvaro Lozano M, Makela M, Marchisotto MJ, Meyer R, Mills C, Nilsson C, Nowak-Wegrzyn A, Nurmatov U, Pajno G, Podestà M, Poulsen LK, Sampson HA, Sanchez A, Schnadt S, Szajewska H, Van Ree R, Venter C, Vlieg-Boerstra B, Warner A, Wong G, Wood R, Zuberbier T, Roberts G; GA2LEN Food Allergy Guideline Group; GALEN Food	• Coordinated the working group on immunotherapy. • Responded to queries from a methodologist. • Took part in the discussion of the findings of the systematic review and put together summary tables based on the GRADE approach. • Participated in the consensus process, voting of recommendations.	• Evidence-based guideline about management of food allergy written with patient involvement.

Additional research outputs.

Publication	Contribution by doctoral candidate	Link to the PhD thesis
Allergy Guideline Group. Managing food allergy: GA2LEN guideline 2022. *World Allergy Organ J*. 2022 Sep 7;15(9):100687.	• Provided feedback on the manuscript.	
Muraro A, Worm M, Alviani C, Cardona V, DunnGalvin A, Garvey LH, Riggioni C, de Silva D, Angier E, Arasi S, Bellou A, Beyer K, Bijlhout D, Bilò MB, Bindslev-Jensen C, Brockow K, Fernandez-Rivas M, Halken S, Jensen B, **Khaleva E,** Michaelis LJ, Oude Elberink HNG, Regent L, Sanchez A, Vlieg-Boerstra BJ, Roberts G; European Academy of Allergy and Clinical Immunology, Food Allergy, Anaphylaxis Guidelines Group. EAACI guidelines: Anaphylaxis (2021 update). *Allergy*. 2022 Feb;77(2):357-377.	• Took part in the discussion of the findings of the systematic review • Put together summary tables based on the GRADE approach. • Coordinated update of the guideline, took part in the consensus process, voting of recommendations and provided feedback on the manuscript.	• Evidence - based guideline about management of anaphylaxis written with patient involvement.
Halken S, Muraro A, de Silva D, **Khaleva E,** Angier E, Arasi S, Arshad H, Bahnson HT, Beyer K, Boyle R, du Toit G, Ebisawa M, Eigenmann P, Grimshaw K, Hoest A, Jones C, Lack G, Nadeau K, O'Mahony L, Szajewska H, Venter C, Verhasselt V, Wong GWK, Roberts G; European Academy of Allergy and Clinical Immunology Food Allergy and Anaphylaxis Guidelines Group. EAACI guideline: Preventing the development of food allergy in infants and young children (2020 update). *Pediatr Allergy Immunol*. 2021 Jul;32(5):843-858.	• Took part in the discussion of the findings of the systematic review and put together summary tables based on the GRADE approach. • Participated in the consensus process, voting of recommendations and provided feedback on the manuscript.	• Evidence based guideline for prevention of food allergy in infants and young children which was written with patient involvement.

Publication	Contribution by doctoral candidate	Link to the PhD thesis
de Silva D, Singh C, Muraro A, Worm M, Alviani C, Cardona V, DunnGlvin A, Garvey LH, Riggioni C, Angier E, Arasi S, Bellou A, Beyer K, Bijlhout D, Bilo MB, Brockow K, Fernandez-Rivas M, Halken S, Jensen B, **Khaleva E,** Michaelis LJ, Oude Elberink H, Regent L, Sanchez A, Vlieg-Boerstra B, Roberts G; European Academy of Allergy and Clinical Immunology Food Allergy and Anaphylaxis Guidelines Group. Diagnosing, managing and preventing anaphylaxis: Systematic review. *Allergy.* 2021 May;76(5):1493-1506.	• Took part in the data extraction, discussion of the findings and provided feedback on the manuscript.	• Systematic review on diagnosing, managing and preventing anaphylaxis which was written with patient involvement.
de Silva D, Halken S, Singh C, Muraro A, Angier E, Arasi S, Arshad H, Beyer K, Boyle R, du Toit G, Eigenmann P, Grimshaw K, Hoest A, Jones C, **Khaleva E,** Lack G, Szajewska H, Venter C, Verhasselt V, Roberts G; European Academy of Allergy, Clinical Immunology Food Allergy, Anaphylaxis Guidelines Group. Preventing food allergy in infancy and childhood: Systematic review of randomised controlled trials. *Pediatr Allergy Immunol.* 2020 Oct;31(7):813-826.	• Took part in the data extraction, discussion of the findings and provided feedback on the manuscript.	• Systematic review on prevention of food allergy in children which was written with patient involvement.
Linked to chapter 2: Patient voice about outcomes for allergy and asthma.		
Vazquez-Ortiz M, **Khaleva E,** Mukherjee S, Infante S, Meyer J, LeFew A, Yuan Q, Martinon-Torres F, Knibb RC. Challenges and unmet needs in FPIES from the parents and adult patients' perspective: An international survey. *J Allergy Clin Immunol Pract.* 2023 Apr;11(4):1306-1309.e2.	• Took part in drafting of the survey. • Qualitative analysis of the survey comments in duplicate. • Provided feedback on the manuscript.	• Survey of perspectives of patients with FPIES and their parents on challenges and unmet needs to improve outcomes.

Additional research outputs.

Publication	Contribution by doctoral candidate	Link to the PhD thesis
Vazquez-Ortiz M, Gore C, Alviani C, Angier E, Blumchen K, Comberiati P, Duca B, DunnGalvin A, Garriga-Baraut T, Gowland MH, Egmose B, Knibb R, **Khaleva E,** Mortz CG, Pfaar O, Pite H, Podesta M, Santos AF, Sanchez-Garcia S, Timmermans F, Roberts G. A practical toolbox for the effective transition of adolescents and young adults with asthma and allergies: An EAACI position paper. *Allergy*. 2023 Jan;78(1):20-46.	• Involved in the acquisition of data including search, analysis and interpretation of data. • Provided feedback on the manuscript.	• Toolbox for effective transition care of adolescents and young adults with asthma /allergies written with patient input to improve outcomes.
Roberts G, Vazquez-Ortiz M, **Khaleva E,** DunnGalvin A, Gore C, Marchisotto MJ, Mortz CG, Pfaar O, Sánchez A. The need for improved transition and services for adolescent and young adult patients with allergy and asthma in all settings. *Allergy*. 2020 Nov;75(11):2731-2733.	• Help in drafting of the manuscript. • Provided feedback on manuscript.	• Editorial on the need to improve transition care for adolescents and young adults with asthma /allergies written with patient input.
Roberts G, Vazquez-Ortiz M, Knibb R, **Khaleva E,** Alviani C, Angier E, Blumchen K, Comberiati P, Duca B, DunnGalvin A, Garriga-Baraut T, Gore C, Gowland MH, Hox V, Jensen B, Mortz CG, Pfaar O, Pite H, Santos AF, Sanchez-Garcia S, Timmermans F. EAACI Guidelines on the effective transition of adolescents and young adults with allergy and asthma. Allergy. 2020 Nov;75(11):2734-2752.	• Contributed to the guideline development including concept and design. • Took part in the acquisition of data including search, analysis, interpretation of data. • Provided feedback on the manuscript.	• European guideline on the effective transition of adolescents and young adults with allergy and asthma written with patient input to improve outcomes.

Publication	Contribution by doctoral candidate	Link to the PhD thesis
Linked to chapter 3: Development of patient-centred outcome measures for severe asthma.		
Mathioudakis AG**,* Khaleva E,*** Fally M,* Williamson PR, Jensen JU, Felton TW, Brightling C, Bush A, Winders T, Linnell J, Ramiconi V, Coleman C, Welte T, Roberts G, Vestbo J. Core outcome sets, developed collaboratively with patients, can improve the relevance and comparability of clinical trials. Eur Respir J. 2023 Apr 3;61(4):2202107.	• Conception and writing the manuscript. * Joint first authorship.	• Editorial on the need to develop core outcome sets with patient input to improve relevance and comparability of clinical trials.
Rattu A, **Khaleva E,** Brightling C, Dahlén SE, Bossios A, Fleming L, Chung KF, Melén E, Djukanovic R, Chaudhuri R, Exley A, Koppelman GH, Bourdin A, Rusconi F, Porsbjerg C, Coleman C, Williams C, Nielsen H, Davin E, Taverner P, Romagosa Vilarnau S, Roberts G; 3TR Consortium Respiratory Work Package. Identifying and appraising outcome measures for severe asthma: a systematic review. *Eur Respir J.* 2023 Apr 3;61(4):2201231.	• Helped to develop literature searches, screen the records, data extraction and COSMIN assessments in duplicate with A. Rattu, PhD student, University of Southampton. • Helped in analysis of modified Delphi exercise, coordination of multi-stakeholder meetings and online voting with A. Rattu, PhD student. • Helped in drafting of the original manuscript.	• Systematic review of the outcome measures used for assesment of severe asthma.
Bel Imam M, Stikas CV, Guha P, Chawes BL, Chu D, Greenhawt M, **Khaleva E,** Munblit D, Nekliudov N, van de Veen W, Schoos AM; Core Outcome Measures for	• Took part in conception of the study.	• Systematic review underpinning development of

Publication	Contribution by doctoral candidate	Link to the PhD thesis
Food Allergy (COMFA) consortium. Outcomes reported in randomized controlled trials for mixed and non-IgE-mediated food allergy: Systematic review. *Clin Exp Allergy*. 2023 May;53(5):526-535.	• Supported throughout the systematic review process. • Provided feedback on the manuscript.	core outcome measures for food allergy.
Demidova A, Drewitz KP, Kimkool P, Banjanin N, Barzylovich V, Botjes E, Capper I, Castor MAR, Comberiati P, Cook EE, Costa J, Chu DK, Epstein MM, Galvin AD, Giovannini M, Girard F, Golding MA, Greenhawt M, Ierodiakonou D, Jones CJ, **Khaleva E,** Knibb RC, Macit-Çelebi MS, Mack DP, Mafra I, Marchisotto MJ, Mijakoski D, Nekliudov N, Özdemir C, Patel N, Pazukhina E, Protudjer JLP, Rodríguez Del Rio P, Roomet J, Sammut P, Schoos AM, Schopfer AF, Schultz F, Seylanova N, Skypala I, Sørensen M, Stoleski S, Stylianou E, Upton J, van de Veen W, Genuneit J, Boyle RJ, Apfelbacher C, Munblit D; COMFA Consortium. Core Outcome Set for IgE-mediated food allergy clinical trials and observational studies of interventions: International Delphi consensus study 'COMFA'. *Allergy*. 2024 Apr;79(4):977-989.	• Participated in the Delphi surveys. • Guided about development of the outcome measures. • Participated in the consensus meeting. • Provided feedback on the manuscript.	• Consensus on core outcome measures for food allergy.
Linked to chapter 4: Searching for patient-centred definitions of response for severe asthma.		
Coleman C, **Khaleva E,** Rattu A, Frankemölle B, Nielsen H, Roberts G, Williams C; 3TR Respiratory Work Package. Narrative review to capture patients' perceptions and opinions about non-response and response to biological therapy for severe asthma. *Eur Respir J.* 2023 Jan 19;61(1):2200837.	• Led concept development, conducted the literature searchers in duplicate with A. Rattu, PhD student, University of Southampton.	• Narrative review of patient views on (non-) response to biological therapy in severe asthma.

Publication	Contribution by doctoral candidate	Link to the PhD thesis
	• Screened the titles, abstracts, full-text articles in duplicate with A. Rattu. • Provided feedback on the manuscript.	
Charles D, Shanley J, Temple SN, Rattu A, **Khaleva E,** Roberts G. Real-world efficacy of treatment with benralizumab, dupilumab, mepolizumab and reslizumab for severe asthma: A systematic review and meta-analysis. *Clin Exp Allergy*. 2022 May;52(5):616-627.	• Supported development of search strategies. • Provided advice on the systematic review process and feedback on the manuscript.	• Systematic review of real-life data about efficacy of biological treatments in severe asthma.

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Finally, I am also grateful to my family, friends and colleagues for their encouragement and support throughout this journey.

Abbreviations

ACQ..... Asthma Control Questionnaire

ACT.....Asthma Control Test

ADSD.....Asthma Daytime Symptom Diary

ANSD.....Asthma Nighttime Symptom Diary

AQLQ.....Asthma Quality of Life Questionnaire

AYA.....adolescents and young adults

BARS.....Biologic Asthma Response Score

COM.....Core Outcome Measures

COMET.....Core Outcome Measures in Effectiveness Trials

COMSA.....Core Outcome Measures sets for paediatric and adult Severe Asthma

CONFiRM.....CompOsite iNdexes For Response in asthMa

COSMIN.....COnsensus-based Standards for the selection of Measurement Instruments

EAACI.....European Academy of Allergy and Clinical Immunology

EFA.....European Federation of Allergy and Airways Diseases Patients' Associations

ELF.....European Lung Foundation

ERS/ATS.....European Respiratory Society / American Thoracic Society

FDA.....Food and Drug Administration

FeNO.....fractional exhaled nitric oxide

FEV_1.....forced expiratory volume in 1 second

FEOS.....FEV_1, Exacerbations, OCS, Symptoms

GAAPP.....Global Allergy & Airways Patient Platform

GLI.....Global Lung Function Initiative

GMP.....good measurement properties

Abbreviations

GRADE..... Grading of Recommendations, Assessment, Development and Evaluations

ICS.....inhaled corticosteroids

ICER.....incremental cost-effectiveness ratio

ISAR.....International Severe Asthma Registry

Ig.....Immunoglobulin

IL.....interleukin

HCPs.....healthcare professionals

MCID.....minimal clinical important difference

MID.....minimal important difference

mOCS.....maintenance oral corticosteroids

NIHR.....National Institute for Health Research

OCS.....oral corticosteroids

PhD.....Doctor of Philosophy

PPI.....patient and public involvement

PROM.....patient-reported outcome measures

PWG.....patient working group

QALYS.....Quality-Adjusted Life Years

QoL.....quality of life

RCT.....randomised control trial

SR.....systematic review

TF.....task force

3TR.....Taxonomy, Treatments, Targets, and Remission

Chapter 1 Introduction

1.1 Epidemiology and definitions of asthma and allergies

Food allergy, asthma, eczema and hay fever are common allergic conditions in children and adults. They significantly affect quality of life (QoL) and are responsible for both morbidity and mortality.

Asthma is defined as heterogeneous disease characterised by chronic airway inflammation and manifests as wheeze, chest tightness, cough, shortness of breath along with variable expiratory airflow limitation.[1] According to the Global Asthma Network Phase I cross-sectional study, over 27-years there has been a significant increase in percentage point prevalence per decade in ever having asthma (1.25, 95% CI: 0.67 to 1.83) and 1 in 10 children and adolescents had wheeze in the previous year, of whom almost 50% had severe symptoms.[2] Similarly for adults, the overall prevalence of symptoms in adults was 6.6% (0.9–32.7%) for current wheeze and 4.4% (0.9–29.0%) for asthma ever.[3] Up to 10% of adults and 2.5% of children with asthma have severe asthma[4] similarly to data from the international severe asthma registry.[5] According to the 2014 UK National Review of Asthma Deaths, out of 155 deaths from asthma 61(39%) deaths were from severe asthma for patients 4-97 years of age.[6] Data from the multinational cohort study of mortality, all-cause mortality rates ranged from 5.2 to 9.5/1000 person-years (PY) in asthma, and between 11.3 and 14.8/1000 PY in severe asthma.[7]This emphasises the need for better management and monitoring of outcomes in paediatric and adult patients with severe asthma.

Eczema, also known as atopic dermatitis, is an inflammatory skin condition that characterised by intense pruritis and recurrent eczematous lesions.[8] It is associated with increased risk of several allergic comorbidities such as asthma, hay fever and food allergy.[9] Hay fever is characterised by inflammation of the nasal mucosa and conjunctivae and defined by the following symptoms such as discharge, itching, sneezing, nasal blockage or congestion.[10] Based on recent Global Asthma Network Phase I multi-country cross-sectional population-based study, the overall prevalence of hay fever ever in adults 14.4% (2.8–45.7%) and 9.9% (1.6–29.5%) for eczema ever.[3]

Lastly, food allergy is an adverse reaction to food caused by immunological mechanisms.[11] It can lead to severe reactions such as anaphylaxis that involves respiratory and cardiovascular symptoms and requires immediate treatment.[12] According to the recent systematic review that I co-authored, pooled lifetime prevalence of self-reported food allergy is 19.9% (95% CI 16.6-

23.3) and point prevalence is 13.1% (95% CI 11.3-14.8).[13] The prevalence and burden of allergic conditions are often difficult to compare due to heterogeniety in the methodology and outcome measures used.[14,15]

1.2 Patient-centred outcomes in medicine

Randomised controlled trials (RCTs) are the gold standard study design to assess efficacy of different interventions across studies. Usually there is a primary outcome that is of greatest treatment importance and secondary outcomes to evaluate additional beneficial or harmful effects of the intervention. A clinical outcome describes a medical event and relates to changes in patient's health, function or QoL.[16]. Surrogate outcomes may be easier to measure and can be used as a substitute of a clinical outcome**;** their validity is often questionnable.[17] In trials it is important to select the most appropriate domain, that is what to measure (e.g. QoL) and a specific measurement, that is how to measure that domain (e.g. a severe asthma quality of life questionnaire). Further, outcomes can be objective (e.g. lung function) or subjective (e.g. need for rescue medication), and clinician reported or patient-reported outcome measures (PROMs). PROMs are often used to monitor and improve care for individual patients, and in health policies and management to assess performance of healthcare providers.[18,19] The use of PROMs encourages patients to participate in their own care[20] while it provides important information to HCPs about their well-being, needs and symptoms to adapt management if nessesary. Moreover, the use of PROMS not only improve patient-related outcomes at individual level but also at organisational and policy levels[21] and has been encouraged use by the European Medicines Agency and Food and Drug Administration as measures of treatment efficacy.[22,23] For example, the SR on routine collection of PROMs in an oncologic setting showed that 21/23 studies reported positive effect on patient-provider communication; 11/11 studies found strong effect on monitoring of patient symptoms, side effects and toxicity during and after chemotherapy for the outpatients; 15/16 studies reported strong effect on detecting unrecognised problems; 13/17 studies reported strong positive effect on the changes to patient management.[24]

Researchers and clinicians typically lean towards reporting outcomes that are easy to measure, expected to be responsive to the intervention rather than what is important to decision making.[25,26] Without having standardised outcomes, there could be bias towards selective reporting of outcomes that show positive results and detrimentally affect care of patients.[27] Participation of patients in the design and conduct of research has become increasingly important and may be beneficial in generating patient-centred trial designs.[28,29]

Understanding what matters the most for patients is pivotal to achieving the best outcomes for them. However, several papers have highlighted differences between what doctors consider important for patients and what patients actually value.[30,31] This emphasises the need for better understanding of patients' lived experiences of disease and what they want to achieve when interacting with a doctor to facilitate shared decision making. This could be achieved by engagement of patients in research projects, clinical trials and guideline development. Meaningful involvement of patients in research occurs when patients and caregivers are actively taking part in study design, study delivery and dissemination of findings. Several barriers and facilitators for effective partnership have been identified for researches who is planning to involve patients.[32,33] For example, it is important to provide training, clearly explain their roles, research methodology and jargon, listen to patients' needs and build trusting collaboration through understanding their perspectives.[34] Patient engagement in research ensures that research questions and outcomes are relevant to patients, their needs and concerns, and results are shared with relevant groups.[35,36] In turn, patients should feel valued as they support health-care interventions and improve lives of other patients.[37]

1.3 Impact of the patient context on the burden of diseases

Adolescents and young adults (AYA) with allergy and asthma are patients aged 11-25 years.[38] These patients are at high risk of morbidity and mortality with a significant rate of asthma deaths and fatal anaphylaxis.[39,40] For example, children with asthma aged 10–14 years had the highest average annual mortality rate (3.1 deaths per million) when compared to other age groups.[41] Similarly, in the database of 604,279 patients younger than 18 years admitted to intensive care, there were 1989 cases of anaphylaxis of which 19 were fatal with most of the deaths occurred in adolescents (53%).[42] During adolescence, AYA go through rapid biological and social development with changes in levels of autonomy.[38] AYA with allergy and/or asthma face additional challenges around psychological factors, health-related QoL, self-management and adherence to medications.[43] Peer pressure may lead to exposure to smoking, alcohol or trying food allergens which may impact on asthma control and cause life-threatening allergic reactions. It has been shown that psychological, educational, e-health and peer interventions lead to better QoL, asthma symptoms, improvements in inhaler technique and management of asthma symptoms.[44] Therefore, education and support for this age group is vital to ensure they have knowledge and skills to gradually taking responsibility for self-managing their allergic diseases.

A knowledge of the challenges that AYA with allergy and/or asthma face should inform the development of appropriate resources for these patients. Based on recent pan-European survey where I am a first author, most healthcare professionals (HCPs) do not have resources and transitional care guidelines to effectively support AYA.[45] Thus, there was a need to develop first European guideline to help HCPs in managing AYA with allergy and asthma. We published this guideline in 2020.[38]AYA need gradual training (called transition process) to enable them to slowly take responsibility from their parents in managing allergic conditions, communicating with HCP on their own and scheduling medical appointments. In other words, the main outcome should be to support AYA into becoming competent and confident adult patients.[46] Several transition guidelines have been implemented for patients with chronic conditions. For example, transitional care programmes for patients with diabetes mellitus showed significant improvements in glycosylated haemoglobin levels, acute and chronic complications, and rates of follow-up and screening.[24] Further, transition programmes have improved outcomes for patients with cerebral palsy, autism spectrum disorders, type 1 diabetes such as promotion of health self-efficacy, appropriate parent involvement, meeting the adult team before transfer with better autonomy in appointments.[47]

Achievement of key outcomes for transition process is not possible without involvement of AYA with allergy and asthma into research and understanding their perspectives. A recent scoping review has identified that only 22/47 studies reported involvement of patient advocates in the development of clinical practice guidelines, while patients and patient advocates reported in 17/47 studies and general public reported in 2/47 studies.[48] Only half (26/42) of identified guidelines involved patients in question identification and even less (18/42) in review drafting. This shows underrepresentation of patient and public involvement (PPI) in guideline development. Qualitative interview study showed that inclusion of patients lead to identification more key clinical issues that were not mentioned by HCPs thus broaden the scope of a guideline and patient-centerdness.[49] Several frameworks have been developed to help researchers in meaningful involvement of patients in guideline development and implementation.[50-52] Involvement of AYA was my starting point in inclusion of patients in outcome research and evaluating their contributions. PPI in guideline development in allergy and asthma is discussed in Chapter 2.

1.4 Patient-centred outcomes in severe asthma

Severe asthma requires treatment with high dose of inhaled corticosteroids (ICS) and additional controllers and/or oral corticosteroid (OCS) to prevent it from becoming 'uncontrolled'.[53] Patients with severe asthma experience many exacerbations and admissions, use more healthcare resources and have poor QoL.[54,55] Short-term courses and long-term daily OCS are

often lead to adverse events such as bone fractures, osteoporosis and cardiovascular disease.[56,57] This further adds to the burden of severe asthma and associated healthcare costs.

Severe asthma has different patterns of airway inflammation such as type 2 low or high[58] which are important to distinguish to guide therapy and make a successful management plan. Type two low- inflammation asthma is characterised by neutrophilic and paucigranulocytic inflammation while type two high-inflammation is eosinophilic airway inflammation with high blood eosinophil count or increased level of fractional exhaled nitric oxide (FeNO).[59] If there is a mix of eosinophilic and neutrophilic airway inflammation it is defined as mixed granulocytic asthma.[59] Raised interleukin (IL)-4, IL-5 and IL-13 levels are typically seen in type two high asthma.[60] Type two inflammation is usually suppressed by treatment with ICS or OCS. However, in some patients with severe asthma eosinophilic airway inflammation persists despite good adherence and maximal dose of corticosteroids.

Biological therapies are monoclonal antibodies that target key inflammatory cytokines involved in pathogenesis of severe asthma.[61] These are expensive add-on therapies for patients who do not respond to traditional asthma medicines such as corticosteroids.[62,63] Prior to initiating biological treatment, it is important to confirm asthma diagnosis, check adherence to ICS and inhaler technique, assess and treat coexisting conditions and avoid exposure of risk factors (e.g. allergens and irritants).[4] Several biological therapies have been developed for use in severe asthma by targeting different cytokines. For example, Benralizumab, Reslizumab and Mepolizumab are anti-IL-5 therapies which target either IL-5 receptor (Benralizumab) or IL-5 itself (Mepolizumab and Reslizumab). Dupilumab is anti-IL-4 and 13 therapy, Omalizumab is anti-immunoglobulin E (lgE) therapy and Tezepelumab targets thymic stromal lymphopoietin.[4] They have different indications, route of administration, safety profile and approved for use age. It has been shown that the incremental cost-effectiveness ratio (ICER) of dupilumab versus standard therapy is 464 000$/ quality-adjusted life-years (QALYS).[64] Similarly, ICER/QALYS value for benralizumab, dupilumab mepolizumab, reslizumab and omalizumab is above the willingness to pay threshold.[65,66] Potential savings included reduction of emergency and primary care visits and hospitalisations.

A recent systematic review of RCTs has shown that Dupilumab reduced exacerbations, use of OCS and rescue medications as well as improved asthma control, QoL and forced expiratory volume in 1 second (FEV_1).[64] Similarly, efficacy and safety of benralizumab, dupilumab and omalizumab was assessed in uncontrolled severe allergic asthma RCTs. These biological therapies reduced annual exacerbations, improved QoL and improved asthma control but not reached minimal important difference (MID).[66] In severe eosinophilic asthma, benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab again reduced exacerbation rate.[65] They

also probably improve asthma control, QoL and FEV_1, without reaching MID.[65] Anti-IL5 biological therapy showed similar effect on clinical outcomes in real-world studies as in RCTs.[67]

When I conducted the real-life systematic review (SR) on the efficacy and effectiveness of biological therapies,[67] I realised a significant heterogeneity in which outcome measures are reported in severe asthma biological RCTs. Even though use of biological therapy has several benefits, there are no head-to-head comparisons of their efficacy and effectiveness. This limits the ability to compare and contrast results leading to ''research waste''. Considerations for choice of biologic have been mostly based on practical considerations and collecting clinical and biological data. These include blood and sputum eosinophils, FeNO, use of OCS, serum total and specific igE, lung function, asthma control, coexisting conditions (e.g. nasal polyps), QoL and number of exacerbations in the previous year.[4] Several algorithms for selection of biological therapy have been published.[68,69] However, it is nessesary to develop a clear approach on how to make a good initial choice of a biologic therapy to avoid further switching, exposure to non-helpful high cost medicines and in turn reduce the risk of patient distrust. There are a few network meta-analysis that compared biological therapies through indirect evidence.[70-73] Some results differed from the results reported in clinical trials.[70] Therefore there is an urgent need to have uniform ways of recording of outcome measures for patients with severe asthma on biological therapies.

Even though a few initiatives have recommended outcome measures for asthma, there is no standardised set of core outcome measures (COM) specifically for severe asthma. A COM set is a minimum group of critically important outcome measures that should be reported in all clinical trials related to a specific condition.[74] To fill this gap, I led the COMSA (Core Outcome Measures for paediatric and adult Severe Asthma) working group to develop patient-centred COM sets to improve synthesis of data and allow meaningful comparisons of different biological treatments in paediatric and adult severe asthma clinical trials (Chapter 3).

1.5 Assessing response to biological therapy in severe asthma

Assesment of response to biological treatment has been a subject of ongoing debate in research and clinical practice. Several studies have defined response to biological therapy; however, they have not only used different outcomes measures, which reinforces the need for standardised COM in severe asthma, but also terminology to define response. Some of the definitions that have been used in the literature include 'deterioration'[75], 'non-response'[76], 'partial response'[77], 'good response'[78] and 'super-response'[76]. Due to heterogeniety of data, a Task Force of HCPs has been formed to develop a traffic-light system to classify patients.[79] It

has reached a consensus for non-responders, intermediate- or super-responders but it has not been developed further.

Several composite outcome measures were then developed such as qualitative tools that measure the level of response achieved (e.g. 'non-response', 'super-response') and quantitative tools that measure how much a patient has improved (or not) from baseline. For example, a quantitative score- FEV_1, Exacerbations, OCS, Symptoms (FEOS) was proposed by adult clinicians from Spain to quantify response based on four clinical parameters.[80] Another simple tool entitled the Biologic Asthma Response Score (BARS) was developed to use in daily practice based on consensus of 8 clinicians in Germany. It consists of exacerbations, OCS and asthma control test (ACT) with defined thresholds for 'good response', 'response' and 'insufficient response'.[81] Thirteen international experts from Interasma Scientific Network platform developed the criteria for 'good response' that should include 3 or more of the following: no or minimal side effects, decrease in the number of exacerbations that require OCS by ≥50%, reduction in use of daily OCS dose ≥50%, and achieve asthma control based on validated questionnaires.[78] Unfortunately, the proposed criteria as well as many others do not define exactly how to measure side effects and what asthma control questionnaire should be used what makes it difficult to compare responses. Lastly, Upham et al have developed the consensus criteria to specifically identify super-responders.[82] They included improvement in three or more criteria where at least two should be major criteria (elimination of exacerbations, major improvement in asthma control, cessation of maintenance OCS).[82]

Recent study looked at data from International Severe Asthma Registry (ISAR) which reported that response to biological therapy depends on patients, outcomes measured as well as type and number of domains included in the definitions.[83] This highlight that clinicians should interpret the current biologic response data with caution. Given multiple definitions, it was useful to explore currently available definitions of (non-) response and better understand their development and quality of psychometric properties by means of the systematic review (Chapter 4). Indeed, the European Academy of Allergy and Clinical Immunology (EAACI) has stated the need for standardisation of definitions of response as a research priority.[84] Having universally defined definitions of response will not only help to compare currently available biological therapies but also in identification of patients who best respond to a particular biological therapy according to asthma phenotype.[85] In turn, this will greatly advance the search for biomarkers of non-response and response to biological therapy to facilitate precision medicine in severe asthma.[86,87] Thus, I looked at gaps identified in the SR from chapter 4 and developed a tool to assess response to biological therapies for severe asthma to fulfil these gaps (Chapter 5).

1.6 Aims and structure of the thesis.

The overarching objective of my PhD was to lay the clinical and methodological groundwork for development of patient-centred outcomes in allergy and asthma.

More specifically, my aims were:

1. To better understand perceptions of adolescents and young adults with allergy and/or asthma and their parents about recommendations for the transition care to improve outcomes and patient care.

2. To develop COM sets for paediatric and adult severe asthma with imput from four stakeholder groups including patients to ensure that the selected COMs sets improve clinical value, comparability and interpretability of RCTs.

3. To review currently available definitions of non-response and response to biological therapy for severe asthma by means of a systematic review. To inform further development of a patient-centred defintions of response to biological therapies as outcomes for severe asthma.

4. To develop the patient-centred tool for standardised assesment of response to biological therapy to use as outcomes for paediatric and adult severe asthma.

The following 4 publications comprising this thesis have been split into four chapters:

Chapter 2: Patient voice about outcomes for allergy and asthma.

- **Publication 1:** Perceptions of adolescents and young adults with allergy and/or asthma and their parents on EAACI guideline recommendations about transitional care: A European survey. **Khaleva E**, Knibb R, DunnGalvin A, Vazquez-Ortiz M, Comberiati P, Alviani C, Garriga-Baraut T, Gowland MH, Gore C, Angier E, Blumchen K, Duca B, Hox V, Jensen B, Mortz CG, Pite H, Pfaar O, Santos AF, Sanchez-Garcia S, Timmermans F, Roberts G. *Allergy*. 2022 Apr;77(4):1094-1104.

Chapter 3: Development of patient-centred outcome measures for severe asthma.

- **Publication 2:** Development of Core Outcome Measures sets for paediatric and adult Severe Asthma (COMSA). **Khaleva** E, Rattu A, Brightling C, Bush A, Bossios A, Bourdin A, Chung KF, Chaudhuri R, Coleman C, Dahlén SE, Djukanovic R, Deschildre A, Fleming L, Fowler SJ, Gupta A, Hamelmann E, Hashimoto S, Hedlin G, Koppelman GH, Melén E, Murray CS, Pilette C, Porsbjerg C, Pike KC, Rusconi F, Williams C, Ahrens B, Alter P, Anckers F, van den Berge M, Blumchen K, Brusselle G, Clarke GW, Cunoosamy D, Dahlén B, Dixey P, Exley A, Frey U, Gaillard EA, Giovannini-Chami L, Grigg J, Hartenstein

D, Heaney LG, Karadag B, Kaul S, Kull I, Licari A, Maitland-van der Zee AH, Mahler V, Schoos AM, Nagakumar P, Negus J, Nielsen H, Paton J, Pijnenburg M, Ramiconi V, Romagosa Vilarnau S, Principe S, Rutjes N, Saglani S, Seddon P, Singer F, Staudinger H, Turner S, Vijverberg S, Winders T, Yasinska V, Roberts G; COMSA Working Group in the 3TR Consortium. *Eur Respir J.* 2023 Apr 3;61(4):2200606.

Chapter 4: Searching for patient-centred definitions of response for severe asthma.

- **Publication 3:** Definitions of non-response and response to biological therapy for severe asthma: a systematic review. **Khaleva E,** Rattu A, Brightling C, Bush A, Bourdin A, Bossios A, Chung KF, Chaudhuri R, Coleman C, Djukanovic R, Dahlén SE, Exley A, Fleming L, Fowler SJ, Gupta A, Hamelmann E, Koppelman GH, Melén E, Mahler V, Seddon P, Singer F, Porsbjerg C, Ramiconi V, Rusconi F, Yasinska V, Roberts G. *ERJ Open Res*. 2023 May 2;9(3):00444-2022.

Chapter 5: Development of a patient-centred tool for assesment of response to biological therapy for severe asthma.

- **Publication 4:** Patient-centred composite scores as tools for assesment of response to biological therapy for paediatric and adult severe asthma. **Khaleva E,** Brightling C, Eiwegger T, Altraja A, Bégin P, Blümchen K, Bossios A, Bourdin A, Ten B.A, Brusselle G, Bumbacea R, Bush A, Casale T, Clarke G, Chaudhuri R, Chung K.F, Coleman C, Corren J, Dahlén SE, Deschildre A, Djukanovic R, Eger K, Exley A, Fleming L, Fowler S, Gaillard E, Gappa M, Gupta A, Haitchi H.M, Hashimoto S, Heaney L, Hedlin G, Henderson M, Hua W, Jackson D, Karadag B, Katelaris C, Koh M, Kopp M, Koppelman G, Kull I, Kurukulaaratchy R, Lee J.H, Mahler V, Mäkelä M, Masoli M, Mathioudakis A, Mazon A, Melén E, Milger K, Moeller A, Murray C, Nagakumar, P, Nair P, Negus J, Nieto A, Papadopoulos N, Paton J, Pijnenburg M, Pike K, Porsbjerg C, Rattu A, Rupani H, Rusconi F, Rutjes N, Saglani S, Seddon P, Siddiqui S, Singer F, Tajiri T, Turner S, Upham J, Vijverberg S, Wark P, Wechsler M, Yasinska V, Roberts G on behalf of the 3TR asthma definition of response working group. *Eur Respir J, 2024, Nov 21:2400691* in press.

Figure 1 shows coherence of each of the four publications that form this PhD. Each chapter is accompanied by summaries of each publication and extended discussion at the end. A full copy of each publication is included in Appendices.

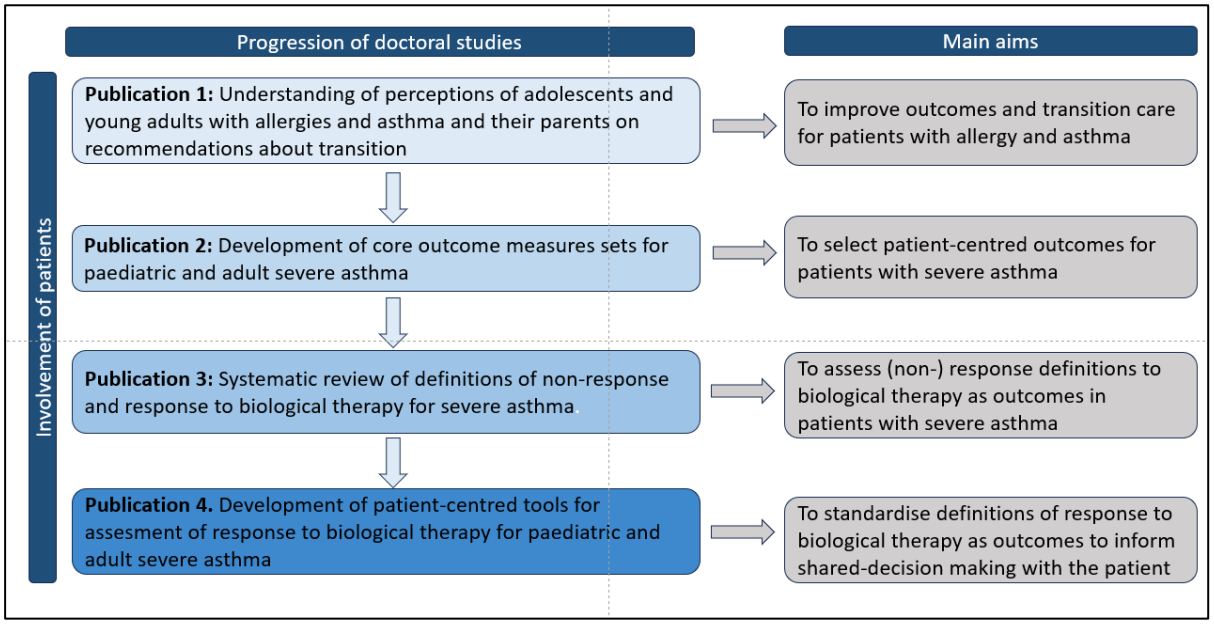

Figure 1 Coherence of publications included in the thesis.

In addition to these four publications, I have published a number of other papers in the last 4 years which are liked in part to this thesis. These are listed in research contributions and outputs (Table i).

Chapter 2 Patient voice about outcomes for allergy and asthma

This chapter is based on ‘’Perceptions of adolescents and young adults with allergy and/or asthma and their parents on EAACI guideline recommendations about transitional care: A European survey.’ manuscript **(Publication 1).** It was published in Allergy journal, 2022.[45] Below is the summary of the rationale for this research, short description of methodology, main results and original contributions.

Practice guidelines aim to review the highest quality research and use practical experience to recommend prevention, diagnostic and management pathways. In order to optimise care of patients it is crucial to integrate their needs and views into research studies. However, there are no universal standards for involvement of patients into guideline development.[88] For instance, in the UK at least two patients or layperson must be involved throughout development of a guideline and in all guideline development committees.[89] Nevertheless, it has been shown that patients’ priorities and outcomes discussed during guideline development have enhanced the quality of guidelines produced.[49,90,91]

Given that there were no European guideline about transitional care, the multidisciplinary EAACI Task Force (TF) has reviewed literature about challenges of AYA with allergy and asthma and interventions for AYA to improve transition of these patients.[43,44] After I joined the EAACI TF, this evidence was used to develop generic and allergy-specific recommendations that formed the first European guideline on the effective transition of AYA with allergy and/or asthma.[38] As part of the guideline development process, I conducted an on-line survey to ensure that these recommendations were also important for AYA with allergy and asthma and their parents from across Europe. I invited AYA with allergy and asthma and their parents to complete a multilingual survey. Participants were asked to rate draft recommendations from ‘’not important’’ to ‘’very important’’ and provide suggestions for refining recommendations where nessesary. I received a total of 1210 responses from 24 European countries ((415 (34.3%) AYA and 795 (65.7%) parents)). Patients had a history of different allergic comorbidites. There was agreement among respondents that the proposed draft recommendations are important to them. All draft recommendations achieved the median score of either ‘important’ or ‘very important’. Lastly, qualitative analysis of comments has helped to make recommendations more patient-centred and we then published them as part of the guideline on transition care.[38]

To the best of my knowledge, this survey is the first of its kind to evaluate draft recommendations by patients and their parents through a pan-European survey design. The survey was distributed through national allergy and asthma patient organizations in Europe who then disseminated the link to the survey among their members. In addition, the survey was advertised on social media platforms which allowed better awareness of the survey and reduced selection bias. In order to achieve high response rate, the survey was translated into eight languages. High number of free-text comments analysed in this survey allowed for more in-depth understanding of the patient perspective on recommendations about transitional care of AYA with allergy and/or asthma. Even though, I received more than 1200 responses from participants with a range of allergic conditions from 24 European countries what show good representativeness, it may not have represented the opinions of AYA and their parents in countries where survey was not conducted. Further, although surveys are effective in collecting a wide range of perspectives, they do not allow possible reasons for certain comments and answers to be investigated. Thus, additional qualitative interviews or focus groups would have been helpful to conduct as part of this study.

The results of this survey have contributed to the development of the first European guideline about transitional care of adolescents and young adults with asthma and allergy.[38,46] Furthermore, the results highlighted the benefits of involving patients into guideline development which could be done through involving patient representatives into guideline group such as TF and/or by surveying opinions through on-line questionnaires. Participants suggested how recommendations could be improved further for example when it is best to develop personal action plan and how often it should be reviewed, and also when it is useful to involve psychologist with knowledge of asthma and allergy in the transition care. By conducting the survey, it has ensured that recommendations developed by HCPs and patient representatives are patient-centred and applicable to patients with allergy and asthma and their parents across Europe. It is hoped by harmonising transition practice will improve outcomes and QoL of these patients. (Figure 2)

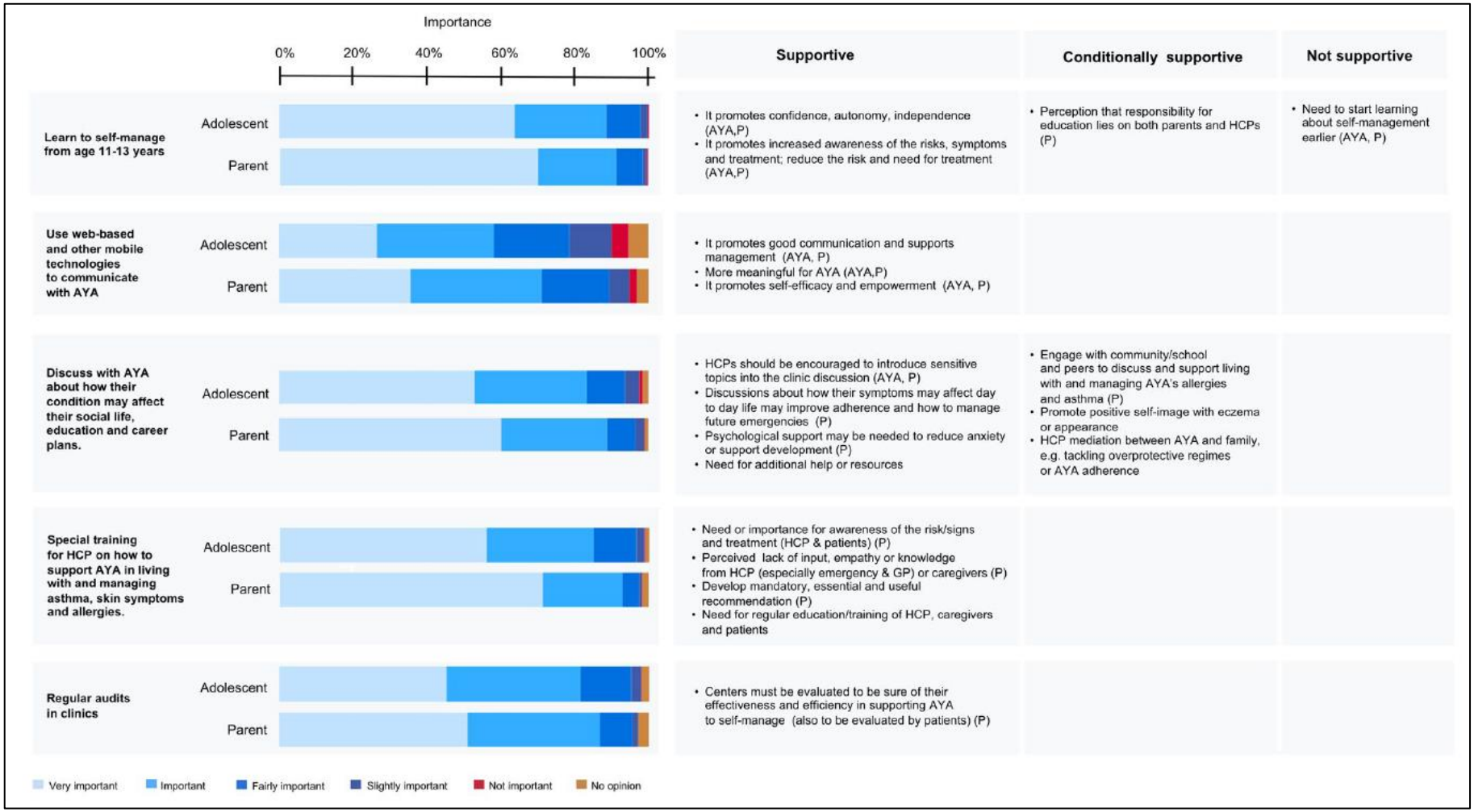

Figure 2 Summary of feedback on generic recommendations. AAI, adrenaline autoinjectors; AYA, adolescents and young adults; GP, general practitioner; P, parents; HCP, healthcare professionals. The thematic map includes themes where the total number of comments for each theme ≥11. Reproduced from Khaleva et al. [45]

Chapter 3 Development of patient-centred outcome measures for severe asthma

Given the significant contributions of patients with allergy and asthma in refining recommendations about translational care, I have continued my patient-centred research to improve patient outcomes in severe asthma. This chapter is based on ‘’Development of Core Outcome Measures sets for paediatric and adult Severe Asthma (COMSA)’ manuscript **(Publication 2).** It was published in European Respiratory Journal, 2023.[92] Below is the summary of the rationale for this research, short description of the methodology, key results and original contributions.

Several outcomes or outcome measures for asthma have been recommended in the NIH series[93-98], coreASTHMA[99], clinical asthma registries[100] and asthma trials[101]; however, there is no agreement on what the COM set for severe asthma should include. Therefore, I developed methodology for the COMSA study based on COMET guideline[102] and recruited participants. A multi-stakeholder consensus process included patients with severe asthma, patient representatives, adult and paediatric clinicians, pharmaceutical representatives and health regulators from across Europe. Given limitations of the survey method in the AYA project, I have recruited adult and youth Patient Working Group (PWG) thought patient organisations, clinics and social media to ensure their participation throughout the project. This is because patients’ voice is important in the development of COM and inclusion of young people is no exeption.[103]

The COMSA sets have been developed through a methodologically robust and multi-national process according to the modified guidance from the Core Outcome Measures in Effectiveness Trials (COMET) initiative.[102] (Figure 3). The COMSA measurement instrument sets were selected from 96 candidate outcome measures through the two-stage Delphi exercise.[104] A systematic review was undertaken to establish their development, validity, and reliability of these outcome measures[104] based on COSMIN (COnsensus-based Standards for the selection of health Measurement Instruments) guidelines.[74] This was conducted with Anna Rattu, PhD student at the University of Southampton.

I involved patients with severe asthma and patient organisation representatives in two ways. Firstly, 14 (adult) and 13 (paediatric) participants formed our patient panels. They were provided with personalised support and involved in multiple training sessions to ensure they feel valued and had the knowledge to give meaningful input to the process. They were also involved in the development of the protocol, discussion of the different outcome measures and conclusions.

This ensured that we had an involved, expert patient voice at the centre of the development process. It has been suggested to incorporate the perspectives of patients from diverse countries in early stages of COM development to ensure that outcomes that matter to patients are not overlooked.[105]

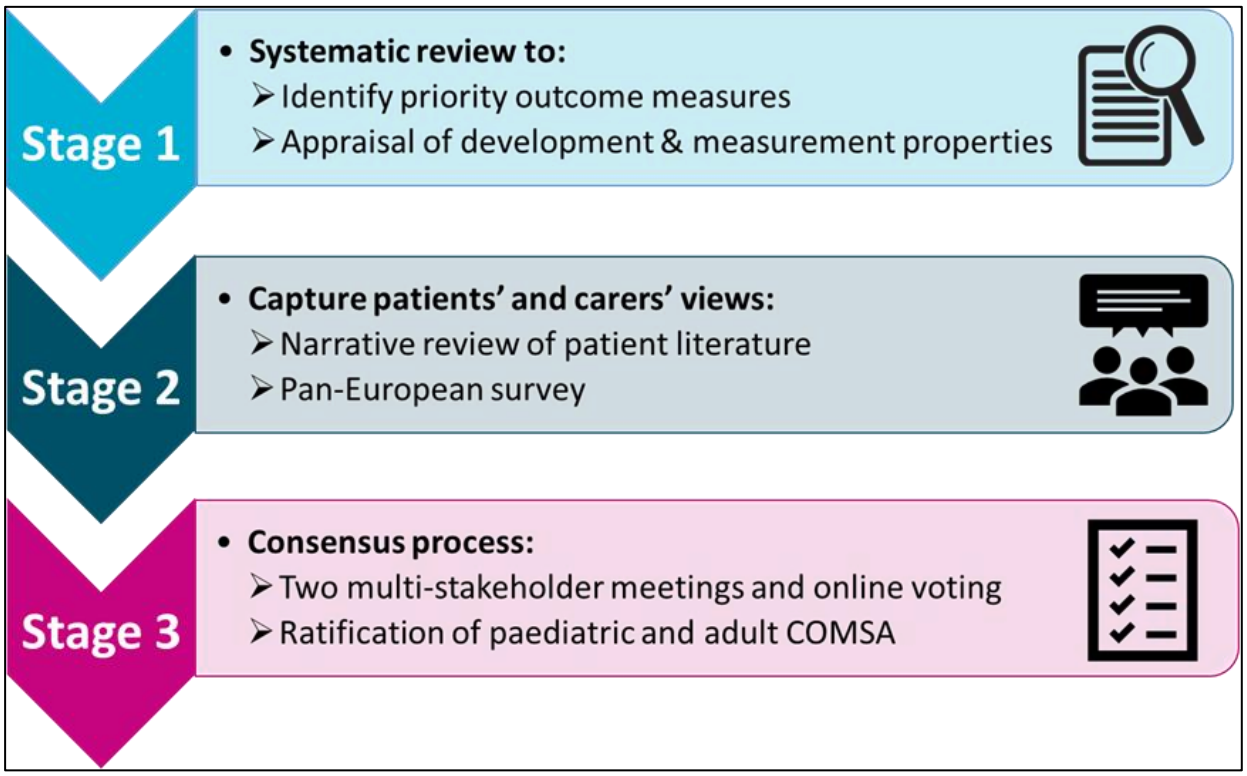

Figure 3 Developmental process of the core outcome measurement sets. COMSA: Core Outcome Measures for children, adolescents, and adults with Severe Asthma. Reproduced from Khaleva et al.[92]

Additionally, in collaboration with European patient organisations I undertook a narrative review of the literature and sought views and opinions from a wider group in the pan-European survey among patients with severe asthma and their parents. The survey was translated into 14 languages and responders were asked about important characteristics of questionnaires and clinical tests with an opportunity to provide further comments. It was disseminated through social media, patient organisations and we only selected those responders whose asthma can be classified as severe according to the European Respiratory Society (ERS)/ American Thoracic Society (ATS) guideline[53]. Given the way that the survey was advertised, I cannot say how many patients were approached; however, more than 200 patients with severe asthma and their carers from Europe completed the survey which allowed wider patient representation in the consensus process. I developed search strategies, performed title and abstract screening for the narrative review, developed the survey and analysed the results.

Evidence from the systematic review, narrative review and pan-European survey was discussed based on the modified Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[106] approach to select COMSA. I organised meetings with participants, voting process and orchestrated multi-stakeholder consensus discussions with European representation. During meetings and online voting, translators were available for patients to prevent any bias and include more patient perspectives. The group reached agreement on five COM for each paediatric and adult COMSA. Briefly, both the adult and paediatric COMSA include FEV_1, frequency of severe asthma exacerbations[101] and maintenance OCS dose. Additionally, the paediatric COMSA includes the Paediatric Asthma Quality of Life Questionnaire[107,108], and ACT[109,110] or Childhood-ACT[111,112], while the adult COMSA includes the Severe Asthma Questionnaire[113,114] and the Asthma Control Questionnaire-6 [115,116]. (Figure 4)

The patient-centred paediatric and adult COMSA are novel as they were specifically developed by four stakeholder groups recruited from across Europe for severe asthma clinical trials. I used the validated COSMIN[74] guideline to assess development, validity and reliability of outcome measures as recommended by COMET.[102] This guideline is similar to the Food and Drug Administration (FDA) guidance on Patient-Reported Outcome Measures[117] but COSMIN gives more detailed assessments about each outcome measure that allows comparisons. Only one asthma PROM is approved by FDA - Asthma Daytime Symptom Diary (ADSD) and Asthma Nighttime Symptom Diary (ANSD) which was not favoured during the Delphi exercise due to daily assessments and the burden on the patients with severe asthma. Additionally, this questionnaire might not be particularly useful for biological trials where any effect might take time to occur. It is hoped that the COMSA outcome measures will be evaluated by the FDA in due course.

Even though most COM have been validated in severe asthma, some do not and were selected based on expert consensus. Also, throughout the project several research gaps have been identified such as development of paediatric QoL questionnaire and questionnaire to capture adherence and side effects of medications that should be fulfilled in future studies. Further, a few additional outcomes have been suggested for consideration in the future.[118] It is important to highlight that COMSA is a minimum set only; other outcome measures could also be included by study investigators according to their research needs. Lastly, using standardised COMSA should increase consistency in reporting of outcome measures, improve comparability of studies with biologics and certainty of evidence to guide policy-making in severe asthma. The results from the trials should impact on the development of new clinical practice guidelines in severe asthma leading to optimisation of patient's care.

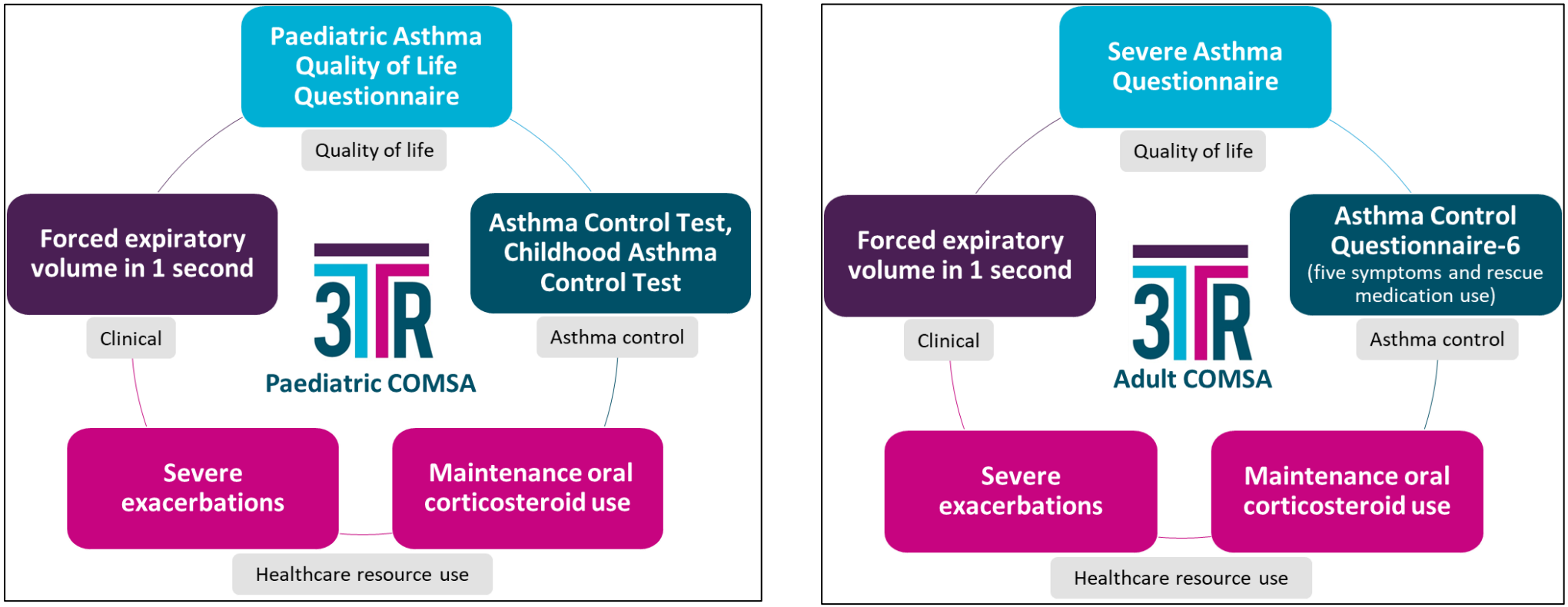

Figure 4 The paediatric and adult core outcome measures sets for severe asthma clinical trials. COMSA: Core Outcome Measures for children, adolescents, and adults with Severe Asthma. Forced expiratory volume in 1 second (FEV_1) should be reported as z-scores using the Global Lung Function Initiative (GLI) predictive equations[119]; annual severe exacerbations as per ATS/ERS definition[101] and maintenance oral corticosteroid (mOCS) use defined as daily or alternate day use ((median (25th, 75th centiles) dose and proportion on mOCS should be reported)). ACQ-6 should be reported as ACQ-5 to describe symptoms and reliever medication use separately. Reproduced from Khaleva et al. [92]

Chapter 4 Searching for patient-centred definitions of response for severe asthma

This chapter is based on ‘’Definitions of non-response and response to biological therapy for severe asthma: a systematic review.’ manuscript (**Publication 3**). It was published in ERJ Open Res, 2023.[120] Below is the summary of the rationale for this research, main results and original contributions.

As now we have patient-centred core outcome measures sets for severe asthma, it is nessesary to search for patient-centred definitions of response to biological therapy for severe asthma and check whether they include the selected COMSA outcomes[92]. As highlighted in recent EAACI severe asthma guideline, there are no standardised criteria for response thus this should be a high research priority gap.[84] Having universally acceptable definitions of response is important for understanding effectiveness of treatment for different stakeholder groups including clinicians, patients and regulatory bodies such the European Medicines Agency (EMA)[121] and the FDA[122].

In this systematic review, I aimed to 1) synthesize evidence about definitions of response to biological therapy in severe asthma; 2) assess their quality of the evidence, and 3) evaluate the development, measurement properties and quality of outcome measures based on COSMIN guidelines.[123-126] The systematic review was restricted to studies where definitions were methodologically developed, defined, and evaluated. I searched four bibliographic databases from inception to 15th March 2021 (PROSPERO: CRD42021211249) and used the modified Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach[123,125,127] to synthesise the results.

Thirteen studies were included in the SR which reported three composite outcome measures[80,128,129], three measures of asthma symptoms[130,131], one asthma control[132] and one QoL[114] (Table 1). Only four outcome measures were developed with patient input[113,133]; none were composite measures. Studies utilised 17 definitions of response: 10/17 (58.8%) were based on Minimal Clinically Important Difference (MCID)[114,129,130] or MID[128,131] and 16/17 (94.1%) had high quality evidence. Variety of biological therapies were used in these studies and response was evaluated at different time points. Unfortunately, the results were limited by poor methodology for development process and incomplete reporting of measurement properties. Most outcome measures were rated ‘very low’ to ‘low’ for quality and none met all criteria for good measurement properties (GMP).

Table 1 Definitions of non-response and response to biological therapy for severe asthma and their quality of evidence.

Reference, year	Scale	Patient input in scale development	Time points from baseline	Method of development of definition of response	Definition of response	Range of scores	GRADE
Composite outcome measures							
Fitzpatrick, 2020[128]	ASSESS	✗	12 months	Distribution-based method	MID= 2 points	0-20 points Higher=worse	⊕⊕⊕◯[A]
Krouse,* 2017[129]	CASI	✗	60 weeks	Anchor-based method	MCID= 1 point	0-18 points Higher=worse	⊕⊕⊕⊕
de Llano, 2021[80]	FEOS	✗	NA	Delphi exercise, conjoint analysis	Response defined according to different thresholds for each outcome measure with respect to baseline. The response ranges from 0 (worsening) to 100 (best).	0-100 points Higher=better	⊕⊕⊕⊕
Asthma symptom outcome measures							
Shen, 2021[130]	ASUI	✓	12 weeks	Anchor-based method	MCID= 0.07 to 0.11	0-1 points Higher=better	⊕⊕⊕⊕
Shen, 2021[130]	ASI	✓	12 weeks	Anchor-based method	MCID= -0.42 to -0.26	0-3 points Higher=worse	⊕⊕⊕⊕
Globe, 2019[131]	ASD**	✓	12,24 weeks	MID: (change −0.5 to −1.0 ACQ) Responder: (change ≤ −1.0 ACQ)	Reported for 12 and 24 weeks: • Mean 7-day score: MID =-0.35 and -0.35; Responder= -0.54 and -0.68 • 7-day symptomatic days: MID: -1.75 and -1.98; Responder: -2.34 and -3.22 • Minimal symptomatic days 1: MID: 1.97 and 2.16; Responder: 2.43 and 3.23 • Minimal symptomatic days 2: MID: 1.02 and 1.36; Responder: 2.31 and 2.56	0-4 points Higher=worse	⊕⊕⊕⊕
Asthma control outcome measures							
Lloyd, 2007[132]	GETE	✗	28 weeks	Physician consensus	• Responder (Complete control; marked improvement of asthma) • Non-responder (Discernible, but limited improvement in asthma, no appreciable change in asthma; worsening of asthma)	0-5 points Higher=better	⊕⊕⊕⊕

Reference, year	Scale	Patient input in scale development	Time points from baseline	Method of development of definition of response	Definition of response	Range of scores	GRADE
Asthma quality of life outcome measures							
Masoli, 2021[114]	SAQ	✓	4,8,12 weeks	Anchor-based method	• MCID (SAQ) = 0.5 points; MCID (SAQ-global) = 11 points	SAQ:1 -7 points; SAQ-global: 0-100 points Higher=better	⊕⊕⊕⊕

ASSESS, Asthma Severity Scoring System; ASUI, Asthma Symptom Utility Index; ASI, Asthma Symptom Index; ASD, Asthma Symptom Diary; CASI, Composite Asthma Severity Index; FEOS, FEV1, Exacerbations, Oral Corticosteroids, Symptoms Score; GETE, Global Evaluation of Treatment Effectiveness; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; MCID, Minimal Clinically Important Difference; MID, Minimal Important Difference; NR, not reported; SAQ, Severe Asthma Questionnaire. *Definition was developed in mild to severe using anchor-based method and then evaluated in biologicals. MID was changed to MCID by the review team. **ASD Symptomatic Days (defined as mean of the 10 ASD daily symptom items ≥1, otherwise non-Symptomatic Day); (2) Minimal Symptom Days-1 (defined as mean of the 10 ASD daily symptom items ≤1 and no single symptom item score > 1, otherwise non-Minimal Symptom Day-1); and (3) Minimal Symptom Days-2 (defined as no single ASD daily symptom item. Tick indicates 'yes' while cross is 'no'. Certainty of evidence was assessed using the GRADE approach.[123,125,127] The reason for downgrading was as follows: A, indirectness. Reproduced from Khaleva et al.[120]

This systematic review has several strengths including using robust methodology such as search in four databases, use of well validated COSMIN[123-126] and GRADE[123,125,127] guidelines. Further, all arbitrary definitions were excluded and only methodologically developed, defined and evidenced were included. Main limitation was that I focused on response to biological therapies only while disregarding evidence from response to non-biological asthma therapies. It may be possible to also learn from the response to other therapies such as to OCS and ICS in severe asthma. It was not possible to conduct a meta-analysis due to low number of studies for each outcome measure and definition of response.

With regards to the original contribution to the field, this systematic review is first in summarising the evidence about methodologically developed, defined and evidenced definitions of response and non-response to biological therapy for severe asthma. It has also identified gaps in the literature and weaknesses in currently available definitions. Another important finding was that there is no composite outcome measure of response that was developed with a patient input. Guideline from the EAACI linked assesment of the response to biological therapy in severe asthma with patient's opinion[84] what highlights the importance of patient's involvement in defining outcomes and response definitions. Thus, the next step was to recruit patients with severe asthma on biological therapy and develop patient-centred paediatric and adult composite definitions of response. Comprehensive assesment of response using a composite measure according to the consensus criteria should allow head-to-head comparison of biologics across studies and provide guidance for further management of patients with severe asthma.

Chapter 5 Development of a patient-centred tool for assesment of response to biological therapy for severe asthma

This chapter is based on ‘’Patient-centred composite scores as tools for assesment of response to biological therapy for paediatric and adult severe asthma.’’[134] manuscript **(Publication 4).** It has been accepted for the publication in European Respiratory Journal. Below is the summary of the rationale for this research, main results and original contributions.

In chapter 3, I developed patient-centred paediatric and adult COMSA. The systematic review from chapter 4 has shown that there are no composite measures of response to biologics for severe asthma that were developed with patient input and have QoL questionnaire. Such composite outcomes consist of a combination of several important outcome measures that help to assess the overall disease progress, can increase statistical precision thus require fewer patients in clinical trials, shorter duration and decreased cost.[135,136] Given the identified gaps in SR, the aim for this project was to develop paediatric and adult CompOsite iNdexes For Response in asthMa (CONFiRM) incorporating core outcome measures from COMSA.

In order to ensure that the developed composite measure of response is universally accepted, I invited international expert healthcare professionals and patients with severe asthma to participate. Participants were asked to contribute to the development of the protocol, patient information sheets and take part in the consensus process to select working definitions of response, develop levels of clinically relevant changes for each outcome measure in the paediatric and adult COMSA. This was followed by assignment of weighting for each COMSA based on relative importance in the assesment of response using multicriteria decision analysis. This group of participants assessed internal validity of both CONFIRM tools. A second group of HCPs was recruited to evaluate the external validity of the CONFIM tools. (Figure 5).

Participants reached a consensus on the five levels of change for each COMSA. They rated severe exacerbations and maintenance OCS as most important in determining response to biologics in both the paediatric and adult CONFiRM tools (Table 2). The higher the CONFIRM score the better improvement after starting a biological (ranging from -31 to 69 points). Both CONFiRM tools demonstrated excellent external validity (Spearman correlation of 0.9 and 0.8 for paediatric and adult CONFIRM, respectively ($p<0.0001$)).

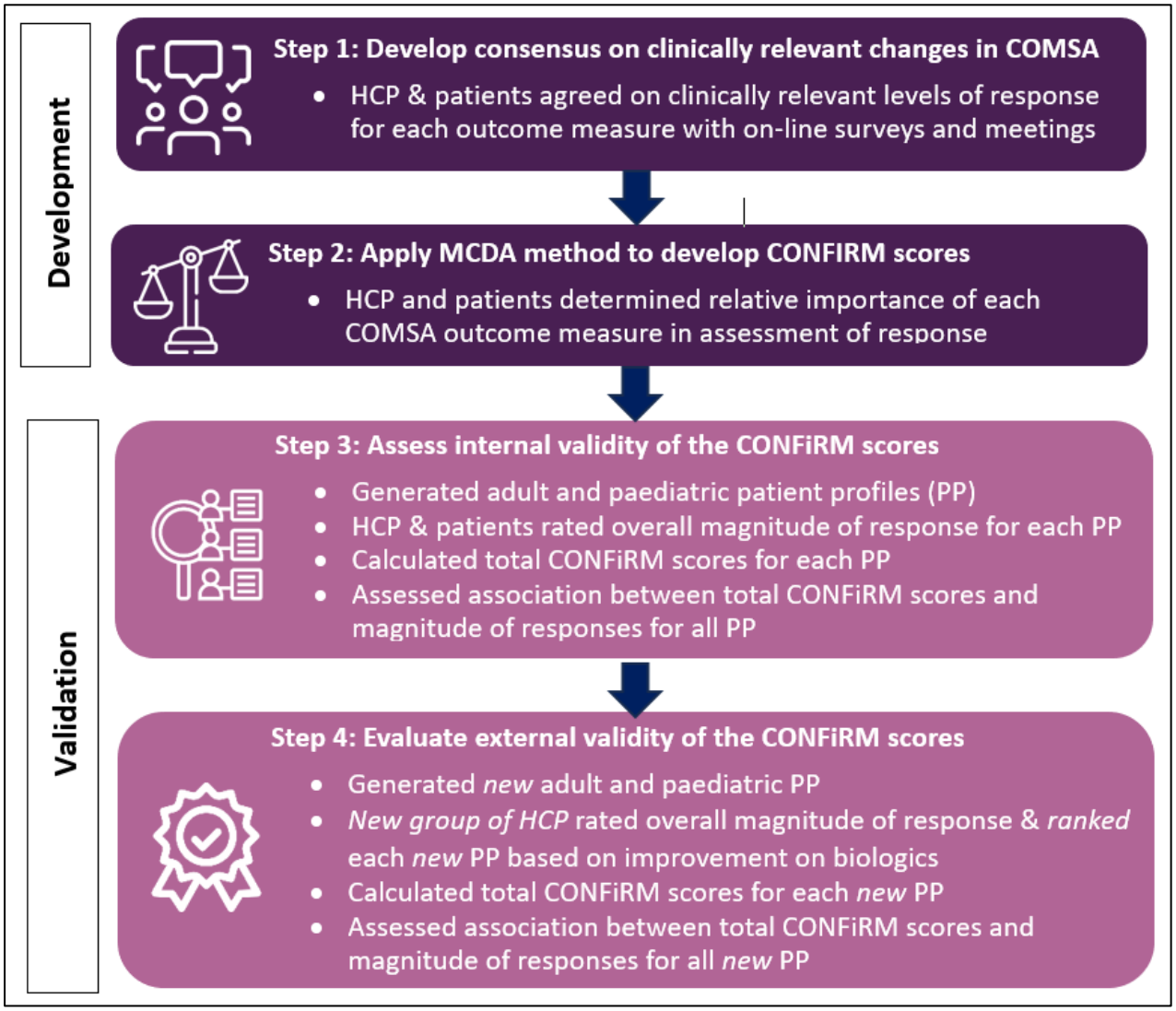

Figure 5 Flow diagram of the CONFIRM development. COMSA, Core Outcome Measures for Severe Asthma; CONFiRM, CompOsite iNdex For Response in asthMa; HCP, healthcare professionals; MCDA, multicriteria decision analysis; PP, patient profiles. Words in italic indicate differences between steps. Reproduced from Khaleva et al.[134]

I would like to acknowledge the following limitations. Profiles were developed from clinical trials from small number of European countries thus might not represent different initiation criteria for biological therapies. Weightings of ACT and C-ACT were assumed to be the same in the composite. The development of the CONFiRM tools has also several strengths. Both CONFIRM tools contain COMSA outcomes that were selected based on their validity and reliability in severe asthma by four stakeholder groups recruited from across Europe. Also, a large number of participants from more than 20 countries took part in the development of the CONFIRM tool. This included diverse experiences of clinicians who manages patients with severe asthma and patients who are currently taking or used to taking biological therapy. I used real patient profiles that were developed from several observational studies with different biologics to capture different patterns of response. Both tools showed good external validity, discriminative ability for substantial and sufficient response.

These two CONFIRM tools are novel as they contain QoL measures and were developed with patients and clinicians using robust methodology. The outcome measures were weighted by participants according to their importance in assessing response to biological therapy. The CONFiRMs should assist clinicians and patients to decide whether to continue a biologic or pursue an alternative treatment. Both CONFIRM tools will also help in assessing effectiveness of novel biologics and enable head-to-head comparisons of different biologics using standardised criteria.

Table 2 CompOsite iNdex For Response in asthMa (CONFiRM) in children and adults.

A. Paediatric CONFiRM

	Select	Points
Severe asthma exacerbations[80]: 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:[80] 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[137]	☐	-5
No change (increase <2 or decrease < 2 points)	☐	0
Increase ≥ 2 points and total score ≤19[109]	☐	4
Increase ≥ 2 points and total score 20 to <23[137]	☐	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%[138]	☐	-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[107]	☐	-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:[80] 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:[80] 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[114]	☐	-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[139]	☐	-4
No change (increase <0.5 or decrease <0.5 points)	☐	0
Decrease ≥0.5 points and total score >1.5[140]	☐	3
Decrease ≥0.5 points and total score from >0.75 to 1.5	☐	6
Decrease ≥0.5 points and total score ≤0.75[140]	☐	9
On treatment FEV_1: change relative to the predicted FEV_1 value at baseline		
Decrease ≥10%[138]	☐	-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.[101] 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.[80]

[#]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.[80]

[◊]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].[138] 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; 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.

Chapter 6 Discussion

This chapter summarise the key findings, implications for further research and clinical practice.

6.1 Summary of key findings

Findings from the original papers included in this thesis are novel and provide important addition to current knowledge in asthma and allergy research. Understanding of views of adolescents and young adults with allergies and asthma and their parents via pan-European survey has allowed development of patient-centred recommendations about transitional care (**Publication 1**). Refined recommendations were then included in first European guideline about transition to guide effective management of these patients. This was the first step in understanding of the importance of patient' views and opinions in asthma and allergy outcomes. Further, inclusion of patients with severe asthma from across Europe was crucial for COMSA development to ensure that patient voice is heard among clinicians, industry representatives and policy makers. From initial pool of 96 'candidate' measures and after Delphi exercises, rigorous CONSMIN assessments and multistakeholder consensus meetings, the selected COMSA consists of five core outcomes. Paediatric and adult COMSA includes severe exacerbations, maintenance OCS use, FEV_1 as a measure of lung function and age specific questionnaires for assesment of asthma control and QoL (**Publication 2**). The next step was searching for definitions of (non-) response to biologics as outcomes in severe asthma, specifically whether any of them were developed with patient input (**Publication 3**). The results have identified several gaps including lack of composite measures of response that contain QoL measure and involvement of patients with severe asthma in their development. Given this unmet need, with help of internationally recruited expert HCPs and patients with lived experience of severe asthma I developed first patient-centred composite outcomes to measure response to biologics using robust methodology. Both paediatric and adult CONFIRM include clinical parameters and QoL measures from COMSA and have good internal and external validity (**Publication 4**).

6.2 How results fit into literature within the discussion of each publication

Patient participation in clinical trials and research is paramount to ensure that patient needs and expectations are met.[141,142] Participants from a range of backgrounds such as age, ethnicity, gender, comorbidities are nessesary to better understand how results will translate into real- word application[143]. However, getting wide patient representation is challenging.[144] First, language barrier

is a well-known issue.[145,146] Thus, there is a need for appropriate translation of materials in different languages, recruitment of multilingual staff or interpreter.[147] Second, lack of access to clinical trials including lack of information for potential eligiable participants.[148,149] This could be tackled by involving patient advocates, patient organisations and community advisory boards into recruitment process.[150] Moreover, people from lower socioeconomic groups and those with least health literacy often most difficult to meaningfully enrol and retain in research studies.[151] Indeed, it has been shown that in the UK, 7.1 million adults read at, or below, the level of an average nine-year- old and more than 4 in 10 adults find it difficult to understand health information written for the public.[152] In order to ensure wide applicability of research findings, researchers should ensure inclusion of 'hard-to reach' population. Thus, several suggestions for research conduct have been outlined including use of simple language, use visuals, videos and social media[152] to help people understand health information while provision of transportation and different types of incentives were found to be useful for recruitment of lower socioeconomic groups.[153] Third is strict inclusion criteria. For example, only around 5% of asthma patients are eligible for clinical trials[154] in contrast with food allergy trials where most patients are eligible, depending on type of allergen and comorbidites. Lastly, inclusion of adolescents as part of the PPI panels and clinical trials. [155] Around 62% of phase 3 trials are currently enrolling adolescents and adults with asthma [155] but evaluation of contributions of adolescents to PPI is difficult.[156] Given that patient input was the key aspect of the thesis, I summarised their involvement and contributions in Table 3.

Table 3 Patient and patient representatives' contributions to this work.

Publication	Recruitment of patients and patient representatives	Contributions of patients and patient representatives
1	• EAACI TF: Patients and patient representatives with allergy and/asthma from Europe were recruited to take part in the EAACI TF. • Survey: Adolescents and young adults, aged 11–25 with allergy and asthma and their parents were recruited for the survey across Europe. The survey link was disseminated through national allergy and asthma patient organizations in Europe to their members (UK, The Netherlands, Italy, Portugal, Spain, Ireland, Germany, Russia, Denmark and France). In addition, the survey was advertised on social media platforms.	• Drafted, piloted and disseminated the survey • Participated in the pan-European survey including provision of free text responses to refine EAACI guideline recommendations on the transition care. • Some patient and patient representatives with allergy and/asthma co-authored the publication.

Publication	Recruitment of patients and patient representatives	Contributions of patients and patient representatives
2	• 3TR Respiratory Adult and Youth PWGS which included adolescents, young adults and adults with severe asthma were recruited by patient organisations from Europe to develop COMSA. • Patient advocacy organisation representatives including ELF, EFA, GAAPP, and Lovexair were recruited to develop COMSA. • Survey: patients aged ≥11 years with severe asthma as well as parents or carers of patients with severe asthma ≥ 6 years were recruited for the survey. The survey was translated into 14 languages. The link to the survey was disseminated through the ELF and EFA websites, newsletters, and websites of patient organisations across Europe, 3TR PWG members' networks and social media.	• Contributed to the development of the protocol, recruitment materials and patient information sheets. • Participated in the monthly calls and discussions of outcome measures. • Drafted and piloted the pan-European survey to better understand opinions of patients with severe asthma and their parents about the most important outcome measures for severe asthma, and dissemination of the survey. • Participated in the narrative review of perceptions of patients on the most important outcomes for severe asthma. • Participated in the Pan-European survey. • Participated in Delphi exercise and consensus meeting to finalise the paediatric and adult COMSA. • Some patients with severe asthma and patient representatives co-authored the publication.
3	• 3TR Respiratory Adult and Youth PWGS which included adolescents, young adults and adults with severe asthma were recruited by patient organisations from Europe to take part in the SR panel. • Patient advocacy organisation representatives including ELF, EFA, GAAPP, and Lovexair took part in the SR.	• Reviewed results of the systematic review about definitions of response to contribute to the COMSA and CONFIRM development. • Some patients with severe asthma and patient representatives co-authored the publication.

Publication	Recruitment of patients and patient representatives	Contributions of patients and patient representatives
4	• 3TR Respiratory Adult and Youth PWG which included adolescents, young adults and adults with severe asthma from Europe were recruited by patient organisations from Europe to take part in development of CONFIRM. • Patient advocacy organisation representatives including ELF, EFA, GAAPP, and Lovexair to take part in development of CONFIRM. • People from across the globe 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 recruited internationally by social media, through clinics (outside of the UK) and patient organisations.	• Contributed to the development of the protocol, recruitment materials and patient information sheets. • Participated in the development of the working definitions of response. • Participated in the narrative review of perceptions about response definitions to biological therapy in severe asthma. • Participated in the monthly calls and discussion of the CONFiRM development. • Participated in surveys, meetings and consensus meetings to finalise the CONFIRM. • Some patients with severe asthma and patient representatives co-authored the CONFIRM and narrative review publications.

EAACI: European Academy of Allergy and Clinical Immunology; PWG: Patient Working Groups; ELF: European Lung Foundation; EFA: European Federation of Allergy and Airways Diseases Patients' Associations; GAAPP: Global Allergy & Airways Patient Platform; CONFiRM: CompOsite iNdexes For Response in asthMa; COMSA: Core Outcome Measures sets for paediatric and adult Severe Asthma; TF- Task Force.

There are a few initiatives that are either currently ongoing or recently finalised core outcome sets or core outcome measures sets in allergy and asthma. For example, core outcome measures for food allergy (COMFA)[157], children with acute exacerbations of asthma[158,159], severe asthma[92,160], moderate to severe asthma[99], severe asthma registry,[161] asthma patient registries and clinical practice[162], clinical trials in childhood asthma,[163] food allergen immunotherapy[164] and NIHR asthma outcomes[93-98,165]. All of them are registered on the COMET database but not all followed the COMET guidance[26] for development of COS and COM. Table 4 summarises methodology and main results of COS or COM related to severe asthma.

Table 4 Core outcome and core outcome measures sets in severe asthma.

Author, year Purpose	Methodology	Participants	Selected core outcomes/ outcome measures
Khaleva E, 2023[92] Severe asthma clinical trials (COMSA)	1. SR of outcomes and assesment of measurement properties and development 2. Delphi exercise 3. Narrative review and pan-European survey among patients with severe asthma/cariers 4. Consensus meetings	108 participants from across Europe: • Clinicians • Patients with severe asthma /their carers and patient advocates • Industry • Health regulators	5 core outcome measures for paediatric and adult severe asthma, respectively: • Severe exacerbations • Maintenance OCS use • FEV_1 • Asthma control questionnaire (ACT,C-ACT/ ACQ-6) • Quality of life questionnaire (PAQLQ/SAQ)
Tejwani V, 2021[99] Moderate to severe phase 3 and 4 clinical trials (coreASTHMA)	1. Literature review 2. Delphi exercise 3. Consensus meeting	45 participants recruited internationally: • Patients and patient advocates • Clinicians and researchers • Life science companies • Payers and HTA • Regulators	• Severe asthma exacerbation • Change in asthma control • Asthma-specific or severe asthma-specific quality of life • Asthma-specific hospital stay (ie, >24-hour stays at any level of care) or admission • Asthma-specific emergency department visit
Martínez-Moragón E, 2023[160] Severe asthma patient follow up	1. SR 2. Focus group with patients 3. Nominal group with clinicians 4. Delphi exercise 5. Consensus meeting	63 clinicians and 5 patients from Spain	• ACT • mini AQLQ • mMRC dyspnea scale • TAI • MMAS • EQ-5D
Bulathsinhala L ,2018[161] International severe asthma registry	1. Delphi exercise 2. Consensus meeting	27 clinicians recruited internationally	• Patient details • Occupation • Medical history + exacerbations • Comorbidites • Blood/sputum eosinophils, lgE count • Diagnostics (Chest CT, DEXA) • Lung function parameters and FeNO • SPT, specific lgE • Asthma control (GINA asthma control questionnaire) • Asthma medications • Adherence • Management plan

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Questionnaire; COMSA, Core Outcome Measures set for Severe Asthma, CT, computerized tomography; DEXA, Dual Energy X-ray Absorptiometry; EQ-5D, European Quality of Life-5 Dimensions; FEV_1, forced expiratory flow in 1 s; GINA, Global Initiative for Asthma; HTA, health technology assessors; Mini-AQLQ: Mini Asthma Quality of Life Questionnaire; mMRC: Medical Research Council modified Dyspnea Scale; MMAS: Morisky-Green Medication Adherence Scale; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; SAQ, Severe Asthma Questionnaire; SR, Systematic Review.

Apart from COMSA consortium, none of the currently available core outcomes measurement sets for severe asthma were assessed based on the COSMIN[74] guideline and published according to the Core Outcome Set–Standards for Reporting statement.[166] In contrast with 21 outcome measures that have been selected for use in asthma patient registries, [161] COMSA has only 5 measures that could be easily collected in any setting. It is important to highlight that COM have only minimal number of outcomes that should be recorded, but clinicians can use other outcome measures that could be important for their study. Both COMSA and coreASTHMA[99] included asthma-specific QoL, exacerbations, asthma control; however, COMSA aimed to select specific instruments to assess QoL and asthma control and also included FEV_1 and maintenance OCS use based on consensus in four stakeholder groups.

Use of COMSA outcome measures were then explored in systematic review of the current definitions of response. Several definitions were proposed such as super-responder which was developed using Delphi technique[82] and FEOS score using multicriteria decision analysis[80]. Identified definitions and composite tools were developed for adults with severe asthma, did not include QoL measure and did not involve patients in the development. Therefore, CONFIRM has fulfilled these gaps including the best validated outcome measures for severe asthma. Indeed, according to the recent survey of patients with severe asthma, measure of QoL was highly ranked by patients with severe asthma[167]. This was further confirmed in interviews of patients who achieved super-response after biological treatment.[168] Therefore, it reinforces the importance of involvement of patients in development of definitions of response, assesment of response to biological therapy and inclusion of QoL questionnaire in the CONFiRM tools.

6.3 Strengths and limitations of the methodology used

Specific strengths and limitations of the methodology used in publications are discussed in the respective chapters and published papers. In this section I will discuss overarching methodology of the thesis.

A major strength of the project was involvement of patients with asthma and/or allergy and their parents throughout the project from across the globe. This ensured that outcomes are important and applicable to a target population. I used several ways to collect their perspectives including a survey method, PPI monthly calls, consensus meetings and online voting. I was able to collect many responses from representatives of different ages, genders and several countries. However, in order for the results to be representative, it would have been useful to include more younger patients and collect additional demographic data about participants such as ethnicity, disability and socioeconomic status as per equality, diversity and inclusion practices. Second, I implemented rigorous and novel methodology using well validated guidelines such as COSMIN and GRADE to rate the evidence. However, even though COSMIN is widely used, it's risk of bias checklist is based on the ''worst score counts'' approach what resulted into downgrading some of the outcomes in the COMSA and definitions of (non-) response to biological therapy systematic review. Given that this is the only guideline that is available for appraising the outcomes, I followed the established recommendations. Third, the team modified COMET methodology for development of COMSA. The original guideline recommends undertake the following four steps 1) to identify all outcomes by means of a systematic review which should be complimented by the qualitative work looking at thouse with lived experience such as patients and their carers; 2) to undertake a multi-stakeholder Delphi process to select the most critical outcomes; 3) to conduct a consensus process to select the core outcomes (what to measure); 4) to select an optimal outcome measure(s) (how to measure) for each core outcome based on the systematic review of all available instruments and quality of their measurement properties. For example, development of the core outcome measures for eczema first reached a consensus on core outcomes which included clinician-reported signs, patient-reported symptoms, QOL, and long-term control. This was followed by selection of instruments and agreement on Eczema Area Severity Index (EASI) for measuring signs; Patient-Oriented Eczema Measure (POEM) and Numerical Rating Scale (NRS) itch peak 24 hours for symptoms; Recap of atopic eczema (RECAP) or Atopic Dermatitis Control Tool (ADCT) for eczema control; lastly for QoL are Dermatology Life Quality Index (DLQI) for adults, Children's Dermatology Life Quality Index (CDLQI) for children, and Infants' Dermatitis Quality of Life Index (IDQoL) for infants.[169]Conducting selection of core outcomes from 'what' to 'how' to measure ensures that all important domains are selected and not limited to a specific number as in the COMSA.

6.4 Implications for research and clinical practice

There are several important implications for both further research and clinical practice arising from the findings of this thesis.

After positive feedback from AYA with allergies and/or asthma and their parents about recommendations **(Publication 1)**, we plan to 1) encourage policy makers to update and adapt

country-specific guidelines on transition care in Europe; 2) facilitate regular audits on the effectiveness of the transitional care, and 3) analyse findings of the survey that we just conducted after 5 years since publishing a guideline to better understand what changes has occurred and what requires further developments in transitional care. It is hoped that by implementing recommendations about transition care into clinical practice, HCPs will help AYA to become confident and competent adult patients who is able to self-manage their allergy and asthma successfully thus improve their long-term health outcomes.

Several unmet needs have been identified when I was working on COMSA development **(Publication 2).** A QoL measure specifically for children and adolescents with severe asthma needs to be developed as currently available QoLs do not assess impairments relevant to young people with severe asthma. Second, many questionnaires are only validated for use in paper form thus further validation for on-line and app are required. Third, use of COMSA should be explored in asthma endotyping and whether it would be helpful in identification of personalised medicines and prediction of treatment responses. As we restricted our aims to a core outcome set for effectiveness studies, there is a need for establishing long-term outcomes, including disease-modifying, in clinical trials involving patients with severe asthma. This is especially important for children due to lack of knowledge about the long-term effects of biological therapies in this population. Lastly, validation of questionnaires measuring side effects of OCS and biologics as well as adherence to severe asthma therapy is needed.

Even though core outcome sets are mainly developed for RCT, they should be adopted in other study types such as systematic reviews and meta-analyses of RCTs. Moreover, COM should be considered for relevant observational studies in order to compare their results with fundings from RCTs. Applicability of COMSA in real life studies have already been shown in Italian observational severe asthma study with different biologics[170] but more prospective studies are needed. The use of COS has increased in rheumatoid arthritis trials[171] but there has been little change in some other health areas.[172] Several barriers for implementation have been identified including complexity in measuring PROMS and resource limitations.[173,174] To overcome that, COMSA has included only easily used outcome measures that are available in each clinic, require minimal burden and cost. Therefore, clinicians should consider using COMSA not only in trials but also in their clinical practice to assess severity of asthma and improve management of patients. Using selected PROMS as part of COMSA such as QoL and asthma control questionnaires will encourage conversation between patients and multidisciplinary team and lead to sharing decision-making, personalise further management plan and ensure personalised quality care.

The next step would include dissemination of COMSA. COMET guideline recommends preparing a dissemination and implementation plan in order to target potential users of COM.[26] Partnership with

relevant stakeholders is needed to support uptake of the COMSA. Regulatory authorities, legislators, research funders and ethics boards should endorse and enforce implementation of COMSA and consider ways to increase uptake including when reviewing funding or regulatory applications. For example, UK National Institute for Health Research (NIHR) guidance for grant applications suggests researchers to search for core outcomes and include in their trial proposal.[175] This strategy from a funding body was found to be helpful to encourage trialists to search for a COS.[176] Apart from promoting COMSA among stakeholders, it is important to gain endorsement from journal editors and systematic review organizations.[177] Other implementation strategies have been suggested by patients/ caregivers and clinicians to boost acceptance of COS and its reporting in trials by demonstrating feasibility and usability.[178] Regular review and updates would help to ensure COMSA consists of the most relevant and important patient-centred outcomes and confirm ongoing validity. Once more data with COMSA outcomes are available, further systematic reviews and meta-analysis would help to compare effectiveness of biologics[179] without head-to-head comparisons to guide policy-making. Plans are in place to disseminate the COMSA and seek endorsement by relevant respiratory and allergy societies.

Given that the definitions of response systematic review **(Publication 3)** was focused on the methodologically developed definitions, the scope of this review was quite narrow and excluded most studies that explore the response in terms of primary and secondary clinical outcomes. It would be interesting to look at change in proportion of participants that achieved MCID for a specific outcome measure e,g, asthma control questionnaire (ACQ) and FEV_1 in QUEST[180] and TRAVERSE[181] studies, rather than only group means. Furthermore, MCID or MID of several well used questionnaires in asthma trials such as ACQ and asthma QoL (AQLQ) have never been specifically assessed in biologics thus require further validation. Nevertheless, definitions of response identified in systematic review should be further explored as primary and secondary outcomes in clinical trials including phase 2 and 3 efficacy studies.

A gap identified in the systematic review led to development of the patient-centred composite tool for assesment of response to biologics in paediatric and adult severe asthma. **(Publication 4).** CONFIRMs included measures selected in the COMSA but weighted according to their relative importance by patient advocates and HCPs. Future studies should identify the appropriate time for assesment of response, scores associated with each magnitude of response and compare improvements in CONFiRMs with improvements in QALYS.

Prior to using CONFiRM in practice, it would require further prospective validation. What is interesting is that different countries have specific recommendations for initiation of biologics with regards to number of exacerbations and levels of biomarkers. Additionally, there are conflicting results of studies when patients with higher levels of biomarkers at baseline and whether it lead to

better response to biologics.[182-184] Thus, application of CONFIRM in real life studies and RCTs could lead to further developments in assessing response. Given that this research is part of 3TR project, 3TR studies such as 3TR-ABC and Dupilumab RCT will utilise CONFIRM tools to provide further prospective validation data. Second, CONFIRM could be used to identify biomarkers that predict response to a biologic as well as early markers of response. This would facilitate personalised and targeted use of biologic approach, better phenotyping of severe asthma and higher quality of care. An attempt has been made to develop a mathematic model to predict a response early in the treatment based on changes in ACQ and AQLQ scores, FEV_1 and the number of exacerbations.[185] Researches concluded that the algorithm was effective in predicting responders (89.9%), but not non-responders (50%). Further research should develop an algorithm using COMSA outcomes and CONFIRM assesment tool in predicting early response based on selected definitions of response such as deleterious, non-response, sufficient-, substantial- or super-response. CONFIRM would also help in developing and assesment of new biological therapies including mastering switching from one therapy to another using standardised assesment.[186] Given that CONFIRM covers multiple dimensions of asthma, it could be used in determining the correct sample size for future clinical trials. Development of a web-based tool and a downloadable calculator should facilitate a widespread use of CONFIRMs in clinical trials, registries and clinical practice and enable head-to-head comparisons of different biologics. Further discussions with policy makers and regulatory bodies are required on how best to use the CONFIRM tool in assesment of response of biologics for severe asthma.

Learning from the CONFIRM's definitions of response such as super-responders could help in exploring the concept of asthma remission.[187] This is a more ambitious long-term goal in severe asthma which might not be achievable in all patients with severe asthma; however, there is no consensus on how asthma remission should be defined.[188-191] In chronic inflammatory conditions such as rheumatoid arthritis remission is clearly defined and could be achieved on biological treatment.[192] If even more expensive next generation of biological therapies were demonstrated to induce remission, they may be more cost-effective in our healthcare system. Though, due to heterogeniety of definitions it is challenging to draw definite conclusions about how effective asthma medicines are in inducing remission. A small group of clinicians (n=8) have developed a general framework for adult asthma remission.[187]However, it lacks wider clinical representation and other stakeholders such as patients and regulators, definitions of key outcome measures and their cut offs. Separate concepts might also be needed to define remission for paediatric asthma and require further research. Other proposals suggested inclusion of ACQ, exacerbation, FEV_1[193] and additionally OCS[194] all of which are part of COMSA and CONFIRM. Therefore, researches could build on the CONFIRM methodology to develop consensus patient-centred definition of remission. The remission criteria will allow us to prioritise therapies that induce remission to minimise patient

burden such as exacerbations and reduction of lung function. Further, it will contribute to studies which aim to identify 'omic handprints' that could predict remission. Thus, remission could be a new outcome-target in novel therapies, inform asthma management and future guidelines.

Lastly, research will only be implemented in clinical practice to patients or lead to further research if there is appropriate dissemination of the findings (Table 5).

Table 5 Dissemination activities of findings from the thesis.

Publications	My presentations
Transition care of AYA with allergy and asthma (Publication 1)	• Roberts G, Khaleva E. Improving adherence. Royal Society of Medicine. Improving transition care for adolescents and young people with asthma and allergies. 20th May 2024, London, UK. • Group facilitator 'Adolescent Mini Masterclass', PAAM meeting, Porto, Porto, 2023. • Group facilitator 'Adolescent Mini Masterclass', EAACI congress, Hamburg, Germany, 2023.
COMSA project (Publication 2)	• Development of a Core Outcome Measures set for children, adolescents, and adults with Severe Asthma (COMSA). Biomedical Research Centre Science Forum, 26th November, 2021. Southampton, UK. • Improving outcomes of patients with severe asthma. Asthma & Allergy Research Hub, May 4th 2023. Southampton, UK. • Core outcomes in asthma. British Society of Allergy and Clinical Immunology meeting. 6th October 2023. Harrogate, UK.
Patient-centred definitions of response for severe asthma (Publication 3)	• The response to biological therapy in asthma. Wessex Paediatric Respiratory Network meeting. 22nd June 2023. Winchester, UK. • Assessing response to biological therapies in severe asthma. Turkish National Congress of Allergy and Clinical Immunology. 30th November 2023. Antalya, Turkey.
CONFiRM (Publication 4):	• Patient-centred composite index for assessment of response to biological therapy for adult severe asthma. European Respiratory Congress (ERS) Congress 2023. Milan, Italy. • Patient-centred composite index for assessment of response to biological therapy for paediatric severe asthma. European Academy of Allergy and Clinical Immunology (EAACI) Congress 2023. Hamburg, Germany. I was awarded 'The best oral presentation award'' at this congress.

AYA: Adolescents and young adults; COMSA: Core Outcome Measures set for children, adolescents, and adults with Severe Asthma. CONFiRM: CompOsite iNdexes For Response in asthMa.

First, several presentations about EAACI transition guideline were done at different European congresses and meetings including AYA hands-on Masterclasses. These practical sessions intended to support the implementation of the recommendations in the clinical environment. We have already trained hundreds of HCPs (I was personally involved along with of members of the TF) in

various important areas in the guideline – for example, improving communication with AYA around allergy and asthma, helping to identify and manage the needs and vulnerabilities of young people during consultations and to improve patient adherence to a management plan. To improve the dissemination, the final recommendations have been translated from medical jargon into more lay terminology and published on the EAACI patient website. In addition to the HCP conferences (see table 5), COMSA results were communicated to patients using more lay terms in various media forms/sites - for example via YouTube video developed with the PWG groupand published on patient organisation websites. The importance of obtaining patient feedback through their HCP is emphasised as needed in the COMSA results sent out regardless of any regular attendance in a severe asthma clinic or taking part in research. All this work is ultimately intended not only to spread the awareness of this novel research among the HCP community but also motivate them to start using the European transitional care guideline and COMSA in their clinical practice and/or research to standardise and improve outcomes in patients with asthma and allergies. I also wanted to ensure that patients' vital contributions are heard, valued, acknowledged and by doing so potentially motivate them to continue feeding back, take part in future research and encourage other patients to do the same thus to improve lives of other patients with allergy and asthma.

6.5 Conclusions.

To conclude, all publications that form this thesis are coherent and provide novel data about patient-centred outcomes in asthma and allergy. The research was based on rigorous methodology including multinational consensus with involvement of several stakeholder groups, multicriteria decision analysis and use of well-validated guidelines such as GRADE[123,125,127] and COSMIN[123]. In addition, patient advocates such as adolescents, young adults, adults and carers of patients with allergy and asthma from across Europe/ world were actively involved in each step of the project to make sure the views of these patients were front and centre. Better consideration of equality, diversity and inclusion of patients in research and guideline development is needed to understand their unmet needs, research priorities, promote shared-decision making and improve clinical care. Gaps highlighted in this research should generate further developments in outcome research in allergy and asthma. It is hoped that by using COMSA and CONFIRM in clinical practice and research it will increase consistency in reporting, improve comparability of data to guide policy making. Further validation of COMSA and CONFiRM tools is needed to better understand response to biologics, improve harmonisation of endpoints, development of more effective medications and improve outcomes of patients with allergy and asthma. Overall, the results of this work highlight the importance of inclusion patients in research as a step forward in achieving standardised patient-centred assesment of outcomes and clinical trial development in allergy and asthma.

Appendix A Core publications

A.1. Summary.

Each publication and supplementary materials are presented with its citation and description of my contributions. Signed declarations of my contributions signed by all co-authors have been shared with the Faculty of Medicine.

A2. Chapter 2. Publication 1.

Citation: Perceptions of adolescents and young adults with allergy and/or asthma and their parents on EAACI guideline recommendations about transitional care: A European survey. **Khaleva E,** Knibb R, DunnGalvin A, Vazquez-Ortiz M, Comberiati P, Alviani C, Garriga-Baraut T, Gowland MH, Gore C, Angier E, Blumchen K, Duca B, Hox V, Jensen B, Mortz CG, Pite H, Pfaar O, Santos AF, Sanchez-Garcia S, Timmermans F, Roberts G. *Allergy*. 2022 Apr;77(4):1094-1104.

My contribution: G Roberts, Vazquez-Ortiz M and myself- survey concept and design. I translated draft recommendations into lay language, members of the EAACI Task Force reviewed and helped in translation into different languages and backtranslation into english. I then conducted quantitative analyses and qualitative analysis in duplicate. Lastly, I interpreted the data, drafted tables and figures, and authored first draft of the manuscript.

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POSITION PAPER

Perceptions of adolescents and young adults with allergy and/or asthma and their parents on EAACI guideline recommendations about transitional care: A European survey

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European Academy of Allergy and Clinical Immunology

Abstract

Background: The European Academy of Allergy and Clinical Immunology has developed a guideline to provide evidence-based recommendations for healthcare professionals to support the transitional care of adolescents and young adults (AYA) with allergy and/or asthma. The goal of this work was to ensure that the draft recommendations are also important for patients.

Methods: We surveyed patients aged 11–25 years with allergy and/or asthma and their parents across Europe between 17 February and 16 March 2020. The multilingual survey was distributed through national allergy and asthma patient organizations in Europe as well as through social media.

Results: A total of 1210 responses from 24 European countries were collected. There were 415 (34.3%) AYA and 795 (65.7%) parents. The majority of AYA (72.3%) and parents (81.9%) were female. Patients had a history of asthma (61.1%), allergic rhinoconjunctivitis (54.1%), food allergy (53.8%), atopic eczema (42.6%) and anaphylaxis (28.8%). All recommendations achieved the median score of either 'important' or 'very important'. The least supported recommendations were the use of joint clinics with both paediatric and adult physicians attending and the use of web-based or mobile technologies for communication with the AYA. The most supported recommendation was checking that the AYA is knowledgeable and compliant with their prescribed medication. Qualitative analysis revealed conditional approval for some recommendations.

Conclusions: There was agreement from patients and parents on the importance of the draft recommendations on transitional care for AYA with allergy and/or asthma and their parents. The recommendations now need to be implemented into clinical practice across Europe.

KEYWORDS
adolescents, allergy, survey, transition, young adults

1 | INTRODUCTION

Transition has been defined as an 'active and evolving process that addresses the medical, psychosocial and educational needs of young people as they prepare to move from child- to adult-centred health care'.[1] Several guidelines on general transitional care have been published by the European Academy of Paediatrics,[2] Canadian Association of Paediatric health centres,[3] American Academy of Pediatrics,[4] and National Institute for Health and Care Excellence.[5] Disease-specific guidelines are also available to optimize transition for adolescents and young adults (AYA) with different long-term conditions.[6–8] Transition programmes have shown significant improvements in patient care during transition leading to low rates of loss of follow-up, high scores for AYA's satisfaction with transition and self-efficacy in managing their disease.[9]

Recently, the European Academy of Allergy and Clinical Immunology (EAACI) published the first European guideline on the effective transition of adolescents and young adults (AYA) with allergy and/or asthma.[10] As part of the guideline development process, an online survey was conducted to ensure the draft recommendations developed by the EAACI Task Force (TF) are important for AYA with allergy and/or asthma and their parents or carers (hereafter referred to as 'parents') across Europe. Involving AYA in refining the European recommendations is an essential step because these are the patients who need to be transitioned and adapt to a new type of care. Understanding what is important to them helps to facilitate a smooth transition, ensure treatment adherence and subsequently improve healthcare outcomes. Parents also play an important role in preparing and supporting adolescents during transition to becoming independent adults. Parents must make a challenging transition themselves from taking full responsibility for their adolescent's healthcare to their child self-managing their disease and becoming a competent patient. It has been shown that assessment of parental perceptions on the transition of AYA with congenital heart defects offered insights into how transition planning could be optimized.[11]

By obtaining the perspective of AYA's and their parents on EAACI draft recommendations for transitional care, we aimed (1) to evaluate the importance of each recommendation independently

for each group and (2) to identify additional factors that need to be included in the 'other considerations' section of recommendations.

2 | METHODS

2.1 | Study design

A quantitative, online, cross-sectional survey was conducted. The survey (available in the Supporting information) was based on recommendations developed by the members of the EAACI Adolescent and Young Adult TF who come from a range of disciplinary and clinical backgrounds, including allergists (specialists and subspecialists), general practitioners, paediatricians, dermatologists, otolaryngologists, adult physicians, nurses, psychologists and patient representatives. Recommendations are based on the results of systematic reviews on the challenges of AYA with allergic conditions,[12] interventions for these patients[13] as well as generic transition recommendations from evidence-based guidelines over the last 5 years. In addition, three rounds of a Delphi survey were conducted among TF members in order to achieve a consensus for D level recommendations.[10]

2.2 | Participants and data collection

We invited AYA, aged 11–25 with allergy and asthma and their parents across Europe who were able to read English, Dutch, Danish, German, Spanish, Portuguese, Italian, French or Russian, to participate in the survey. The survey was distributed through national allergy and asthma patient organizations in Europe (UK, The Netherlands, Italy, Portugal, Spain, Ireland, Germany, Russia, Denmark and France) who then disseminated the link to the survey in SurveyMonkey among their members. In addition, the survey was advertised on social media (eg Facebook, Twitter). Before accessing the questionnaire, potential respondents were informed about the survey's purpose, the organizations conducting the survey and the average time required to complete. Responses were collected between 17th February and 16th March 2020.

2.3 | The questionnaire

The anonymised survey included 24 questions divided between two parts: five questions about demographic information (AYA or parent, age, gender, country and allergic diseases) and 19 questions about the level of importance of each recommendation. Recommendations were divided into five groups, namely (1) generic advice, (2) treatment for allergy and asthma, (3) self-management, (4) psychological issues and help, and (5) support from family, friends and others. Participants were asked to rank the level of importance for each recommendation using a 5-point scale: 1 'Not important', 2 'Slightly Important', 3 'Fairly important', 4 'Important' and 5 'Very Important', plus a 'No opinion' option was available. An average score of at least 2 was set as the level for acceptance of the recommendation. Options for free-text responses were provided. The wording of the questionnaire was carefully checked to ensure it could be understood by this lay audience, translated into eight languages (English, German, Spanish, Portuguese, Italian, Danish, Dutch, French and Russian) and back translated into English to ensure validity and accuracy. Reading age was tested prior to dissemination of the survey to ensure clarity and understanding. A group of target participants also tested the time required to complete the survey, which ranged from 15 to 20 min.

2.4 | Qualitative analysis

Qualitative data analysis was used to summarize free-text comments from AYA and parents. All comments from AYA and parents were analysed separately. Comments in languages other than English were translated by one TF member and checked by a second TF member. Braun and Clarke's steps for thematic analysis were used for analysis.[14] Each comment was coded, and the codes were then combined into themes. In order to ensure that responder views were correctly interpreted, each comment and its code was reviewed in duplicate by patient representatives, clinicians and psychologists from the EAACI TF (EK, GR, CA, RCK, ADG, PC, T. G-B and MHG). Any discrepancies were resolved through discussion and, if necessary, a third reviewer (M.V-O) was consulted. Codes were then split based on the direction of the content: supportive, conditionally supportive or non-supportive (Supporting information).

2.5 | Statistical analysis

All data were collected and analysed using SPSS software version 25.0. Descriptive statistics were used to describe respondent characteristics. Medians with lower and upper quartiles are presented for continuous variables given the distribution of the data. Frequency tables with percentages are provided for categorical variables.

A minimum of 50 responders per country was required for the comparison of data between countries. The comparisons were performed by using the Kruskal-Wallis test. Summary tables were used to represent the results. Data were considered significant if statistical tests produce a p-value of <0.05.

3 | RESULTS

3.1 | Respondent demographics and characteristics

Among 1425 received responses, 215 (16%) were excluded as they were either incomplete or came from outside Europe. A total of 1210 responses from 24 European countries were analysed. The most common countries of residence were Italy (20.7%), Portugal (17.0%), France (15.6%) and Russia (15.4%). There were 415 (34.3%)

AYA and 795 (65.7%) parents. The majority of AYA (72.3%) and parents (81.9%) were female. Patients had a history of asthma (61.1%), allergic rhinoconjunctivitis (54.1%), food allergy (53.8%), eczema (42.6%) and anaphylaxis (28.8%). Most AYA had one (29.7%) or two (26.9%) allergic conditions but 22.0% had more than four allergic comorbidities. Respondents' characteristics are listed in Table 1.

TABLE 1 Demographics of survey responders

All responders ($n = 1210$)	Number (%) of responders
Adolescents and young adults	415 (34.3)
Male	115 (27.7)
Female	300 (72.3)
Parents	795 (65.7)
Male	144 (18.1)
Female	651 (81.9)
Type of allergic disease	
Asthma	739 (61.1)
Allergic rhinoconjunctivitis	655 (54.1)
Food allergy	651 (53.8)
Eczema	515 (42.6)
Anaphylaxis	348 (28.8)
Urticaria	248 (20.5)
Drug allergy	132 (10.9)
Venom allergy	68 (5.6)
Number of allergic diseases[a]	
1	359 (29.7)
2	326 (26.9)
3	257 (21.2)
≥4	266 (22.0)
Countries	
Italy	251 (20.7)
Portugal	206 (17.0)
France	189 (15.6)
Russia	186 (15.4)
United Kingdom	103 (8.5)
Spain	71 (5.9)
Denmark	54 (4.5)
Netherlands	46 (3.8)
Germany	26 (2.1)
Ireland	25 (2.1)
Others[b]	53 (4.4)

[a]Anaphylaxis is not included as a separate condition.

[b]Bulgaria $n = 1$ (0.1%), Greece $n = 1$ (0.1%), Luxembourg $n = 1$ (0.1%), Poland $n = 1$ (0.1%), Romania $n = 1$ (0.1%), Georgia $n = 1$ (0.1%), Azerbaijan $n = 1$ (0.1%), Turkey $n = 1$ (0.1%), Switzerland $n = 6$ (0.5%), Kazakhstan $n = 3$ (0.2%), Belarus $n = 6$ (0.5%), Ukraine $n = 15$ (1.2%) and Belgium $n = 15$ (1.2%).

3.2 | Importance of the recommendations on transitional care

All recommendations were (at minimum) scored as 'important' (median score of 4 on the 5-point scale) (Table 2). The most supported recommendation was that of checking that the AYA are knowledgeable and compliant with their prescribed medication, with 68% of AYA and 77.7% of parents reporting this as 'very important'. The least supported recommendations related to the use of joint clinics with both paediatric and adult physicians attending (only 27.7% AYA and 38.1% parents reported this as 'very important') and the use of web-based mobile technologies for communication with the AYA (only 27.0% AYA and 35.6% of parents reported this as 'very important'). In addition to overall data, a sensitivity analysis showed that the results were similar in individual countries with more than 50 responses (Table S1).

Of the 1356 free-text comments received, 978 (72.1%) were made by parents. Summary of the feedback with all themes from AYA and parents may be found in the Tables S2–S19. Figure 1 and Figure S1 show the key supportive, conditionally supportive and not supportive comments for generic recommendations, Figure 2 presents comments on treatment and self-management of allergy, skin disease and asthma and comments on psychological issues and help, and support from family, friends and others are found in Figure 3. In general, AYA's and parents' feedback was similar (Tables S2–S19). There were some notable exceptions such as parents were more likely to comment that transition should start earlier in adolescence (Table S2).

Almost all comments were supportive with a few conditional ones, which were used to improve the recommendations. For example, respondents suggested that a personal action plan should be developed not only when AYA are about to be transferred to the adults' department, but should instead be utilized at an early stage before adolescence. In addition, it was suggested that the action plan should be regularly reviewed by all HCP involved in the individual's care. With regard to motivational interviewing, participants proposed that active involvement of AYA in discussion would improve self-management of asthma and quality of life. Adolescents suggested that conversation about possible stressful life events that may impact disease control should be explored in a very sensitive way, and that psychological interventions using cognitive behavioural therapy to improve adherence, self-management and symptom control are likely to be most effective for specific patients, for example, those struggling to self-manage their condition. Professionals who support those with difficulties, such as psychologists, should have expertise in allergy and asthma. The family should be enrolled early in the transition process; however, the shift from parent to self-management should be done gradually to support AYA empowerment. Telling friends may be difficult for some and AYA suggested that they should be supported and encouraged to start by talking to a few close friends. Parents added that there should be a balance between autonomy and safety and recognized that it may be challenging for them to reduce control of their child's life.

Key negative comments related to the suggestion that adolescents should learn about self-management before 11 years of age; that the

Appendix A

TABLE 2 The level of importance for each recommendation as regarded by participants

Recommendation	AYA $n = 415$ Median (IQR)	Parents $n = 795$ Median (IQR)
Generic advice		
1. Young people should start to learn how to manage their asthma, allergies and skin disease when they are about 11–13 years old	5 (4,5)	5 (4,5)
2. It is important to think about:		
Making sure that clinics have a plan/special document about how to care for young people as they grow up	5 (4,5)	5 (4,5)
Telling the young person and their parents or carers about how the plan will work and how it will change as they grow up	5 (4,5)	5 (4,5)
Using a checklist to find out when the young person is ready to take more responsibilities for their asthma, allergy and skin disease as they grow up	4 (4,5)	5 (4,5)
Checking that the young person is able to and takes the medicines they have been given	5 (4,5)	5 (5,5)
If the young person has to move across from a children's clinic to one for adults, it would be helpful for them to see both children's and adult's doctors in one clinic transiently while they get used to the change	4 (3,4)	4 (3,5)
The doctors and nurses caring for young people in children's and adult clinics should have regular meetings to discuss their care	4 (3,4)	4 (4,5)
3. Doctors and nurses could use web-based and other mobile technologies such as texts or skype to communicate with the young person	4 (3,4)	4 (3,5)
4. It may be helpful for doctors and nurses to talk to young people about how their asthma, allergies and skin disease may affect their social life (eg when being with friends or family), education and career plans	5 (4,5)	5 (4,5)
5. Doctors, nurses and other medical staff should have special training to help young people with asthma, skin symptoms and allergies	5 (4,5)	5 (4,5)
6. There should be regular checks of how well the clinic works to make sure it is effective and helpful for young people	4 (4,5)	5 (4,5)
Treatment of allergy, skin disease and asthma		
7. The doctors and nurses should try to make the young people's treatment easy to follow	4 (4,5)	5 (4,5)
8. Phone reminders, apps and other methods may be useful to help young people to remember their treatment and take more responsibility for looking after their asthma, skin disease and allergies	4 (4,5)	4 (4,5)
Self-management of allergy, skin disease and asthma		
9. A personal action plan covering what to do would help young people manage their asthma, skin disease or allergies	4 (4,5)	5 (4,5)
10. It would be helpful during the hospital visit to focus on issues and ways to manage asthma, skin disease and allergies where the young person is less confident	4 (4,5)	5 (4,5)
11. Young people and their families might want guidance from doctors and nurses on how to manage their asthma, skin disease or allergies when the young person is at social events (eg sports, celebration, holidays)	4 (3,5)	5 (4,5)
12. Young people could learn from other young people with asthma, skin disease and allergies about how to manage their life	4 (3,5)	4 (4,5)
13. Doctors or nurses should have conversations with young people designed to strengthen their motivation and commitment to improving their asthma management	4 (4,5)	5 (4,5)
Psychological issues and help		
14. Doctors and nurses should look out for young people who feel anxious or depressed as these may affect their asthma, skin disease and allergies	5 (4,5)	5 (4,5)
15. Doctors and nurses should find out if young people have experienced stressful events (such as parents' divorce or bullying) which may affect their asthma, skin disease and allergies	4 (4,5)	4 (4,5)

(Continues)

TABLE 2 (Continued)

Recommendation	AYA $n = 415$ Median (IQR)	Parents $n = 795$ Median (IQR)
16. A psychologist may be able to help young people to manage their asthma, skin disease and allergies better	4 (3,4)	4 (4,5)
Support from family, friends and others		
17. Families should be encouraged to support young people as they start to manage their asthma, skin disease and allergies	5 (4,5)	5 (4,5)
18. Young people should be encouraged to let their friends know about their asthma, skin disease and allergies and how they can help in an emergency	5 (4,5)	5 (4,5)
19. Clinics should recommend reliable websites and other useful sources of information about asthma, skin disease and allergies to young people	4 (4,5)	4 (4,5)

Note: IQR, interquartile range. Potential responses were 1 'Not important', 2 'Slightly Important', 3 'Fairly important', 4 'Important', and 5 'Very Important', plus a 'No opinion' option was available. AYA, adolescents and young adults.

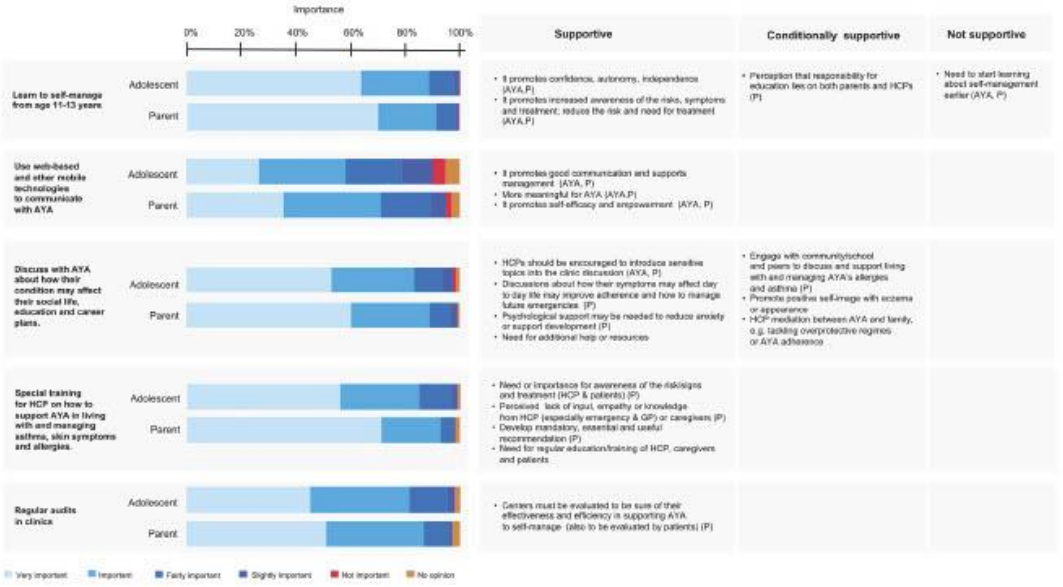

FIGURE 1 Summary of feedback on generic recommendations. AAI, adrenaline autoinjectors; AYA, adolescents and young adults; GP, general practitioner; P, parents; HCP, healthcare professionals. The thematic map includes themes where the total number of comments for each theme ≥11. Information in brackets specifies which group (AYA and/or P) has more than 11 comments in each theme. If none of the groups reported ≥11 comments in the theme but it has ≥11 total number of comments this theme is also included

use of aids to improve adherence might undermine AYA taking responsibility for their care; and some felt that AYA might not be happy to share the details of their allergic diagnoses with their friends.

4 | DISCUSSION

The findings from this pan-European survey support the value of draft guideline recommendations on the transitional care developed by the EAACI Adolescent and Young Adult Task Force for both AYA with allergic conditions and their parents (Figure 4). Conducting this survey in different European countries and health systems demonstrated that the recommendations are understood by AYA/parents and remain relevant. The rich qualitative data set of almost 1400 comments and the thematic analysis of the responses to the open-ended questions provided additional insights on their opinions about each recommendation. From this survey, we were able to further refine the recommendations based on the range of supportive, conditionally supportive and minimal number of non-supportive free-text responses.

This survey contributes to the growing literature on the benefits of patient-centred care and understanding of patient perceptions and views for healthcare decision-making.[15] For example, patient-reported experience measures have been used to guide quality improvement across different settings.[16] Moreover, a set of considerations to engage AYA in research have been proposed[17] and several guidelines on transitional care involved this age group and their parents in the development of guideline recommendations.[6,18]

Survey participants recognized the value of actively monitoring adherence to treatment throughout transition, but did not consider an overlap in care between paediatric and adult HCP to be particularly important. This finding may be because some countries do not have separate paediatric and adult specialists (allergists, dermatologists and respiratory physicians) and care is mostly led by general practitioners or specialists who treat patients of all ages. In contrast, AYA with inflammatory bowel disease rated joint consultation with both HCP as one of the most valuable features of the transition care program.[19] Other methods of communication between HCP and AYA such as web-based, mobile technologies were also considered less important. Research indicates that AYA generally prefer using web-based methods of communications[20] and are less interested in using social media sites for communication with HCP due to privacy concerns.[21] These two less popular recommendations align with other guidelines, which emphasize the importance of suitable use of technology for interaction between patients and HCP[1,5,8] and joint consultations.[8,22]

Limitations inherent in the survey method impacted our ability to investigate possible reasons for our findings. Further qualitative interviews might identify why AYA do not fully support joint care by adult and paediatric HCP or the use of technologies for communication with HCP. Some respondents reported that self-management training should start before 11 years of age. We would agree that is appropriate for some AYA in line with developmentally appropriate healthcare.[23] Some AYA find technological solutions, such as an alarm on a mobile phone, to be very helpful to improve their treatment adherence.[24] Additionally, some AYA reported concerns about what their friends might think if they shared the details of their allergic diagnoses with them, although others reported this as a positive experience with AYA receiving considerable support from their close friends.[25]

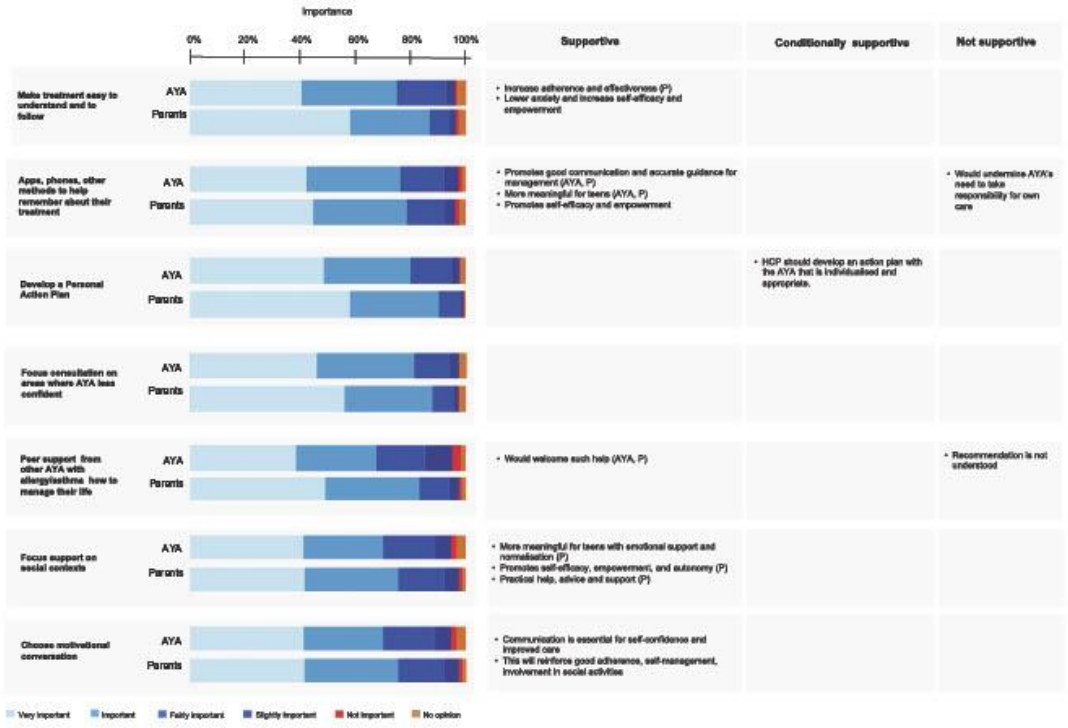

FIGURE 2 Summary of feedback on adherence and self-management recommendations. AAI, adrenaline autoinjectors; AYA, adolescents and young adults; GP, general practitioner; P, parents; HCP, healthcare professionals. The thematic map includes themes where the total number of comments for each theme ≥11. Information in brackets specifies which group (AYA and/or P) has more than 11 comments in each theme. If none of the groups reported ≥11 comments in the theme but it has ≥11 total number of comments this theme is also included

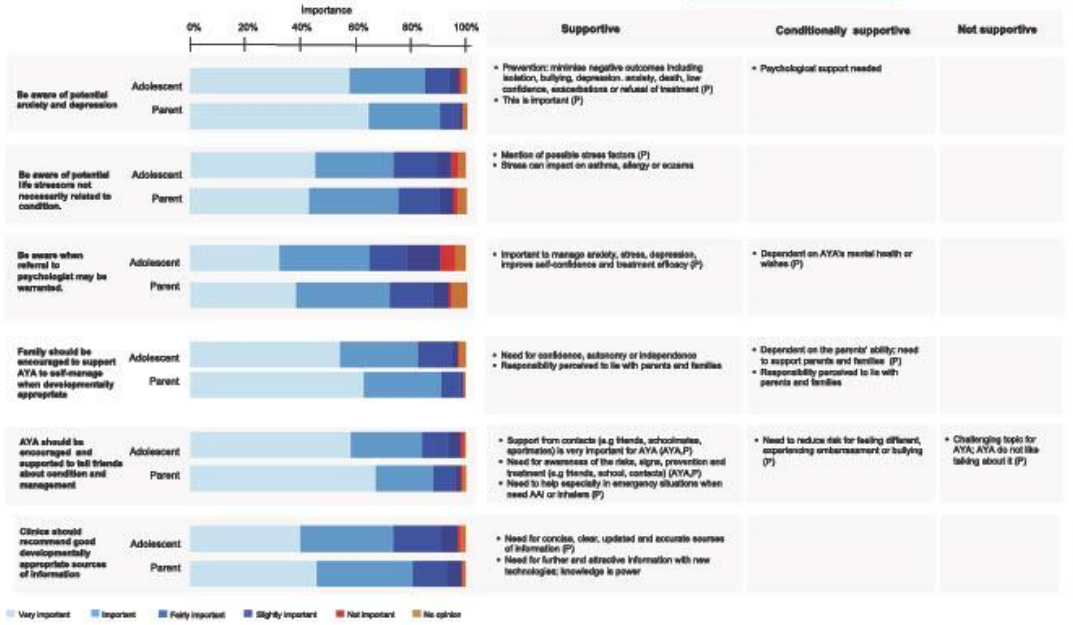

FIGURE 3 Summary of feedback on psychology and support recommendations. AAI, adrenaline autoinjectors; AYA, adolescents and young adults; GP, general practitioner; P, parents; HCP, healthcare professionals. The thematic map includes themes where the total number of comments for each theme ≥11. Information in brackets specifies which group (AYA and/or P) has more than 11 comments in each theme. If none of the groups reported ≥11 comments in the theme but it has ≥11 total number of comments this theme is also included

4.1 | Strengths and limitations of the survey

Although the survey covered most European countries, it may not represent the opinions of AYA and their parents in countries not surveyed. Technical limitations meant that comments were not included for the second recommendation; however, ranking did allow us to assess importance in both groups. The representativeness of the survey is likely to be high given the large number of responses from patients with a range of allergic conditions, and their parents. Furthermore, 29.7% had one and 22% more than four allergic comorbidities. To the best of our knowledge, this survey is the first of its kind to evaluate draft recommendations by patients and their parents through a pan-European survey design, and the high number of free-text comments analysed in this survey allowed for more in-depth understanding of the patient perspective on recommendations concerning transition and transfer of AYA with allergy and/or asthma from paediatric to adult services.

4.2 | Implications

There are several important implications arising from the findings of this survey. Firstly, recommendations on transitional care are important for AYA with allergy and/or asthma and therefore should be implemented within clinical practice across Europe. Secondly, qualitative analysis of comments can help to refine recommendations by allowing for the provision of additional information from the patient perspective.

All generic and allergy-specific recommendations on adherence, self-management, support and psychological help received positive feedback from both AYA with allergies and/or asthma and their parents in Europe. Recommendations are intended to be useful, practical, facilitate local teams to work together and promote transition and transfer where necessary. We would like to emphasise that the application of these recommendations and the effectiveness of the healthcare for AYA with allergies and asthma should be revaluated through regular audits.[10] Assessment should involve AYA and families, as well as policy makers, researchers and government agencies.[26] It is hoped that harmonization of the transition process and practice will improve psychological and physical outcomes as well as the quality of life of these patients.

5 | CONCLUSIONS

This pan-European survey showed that adolescents and young adults with allergy and/or asthma and their parents find draft EAACI recommendations on transitional care for these conditions important or very important. Qualitative analysis of responses to open-ended

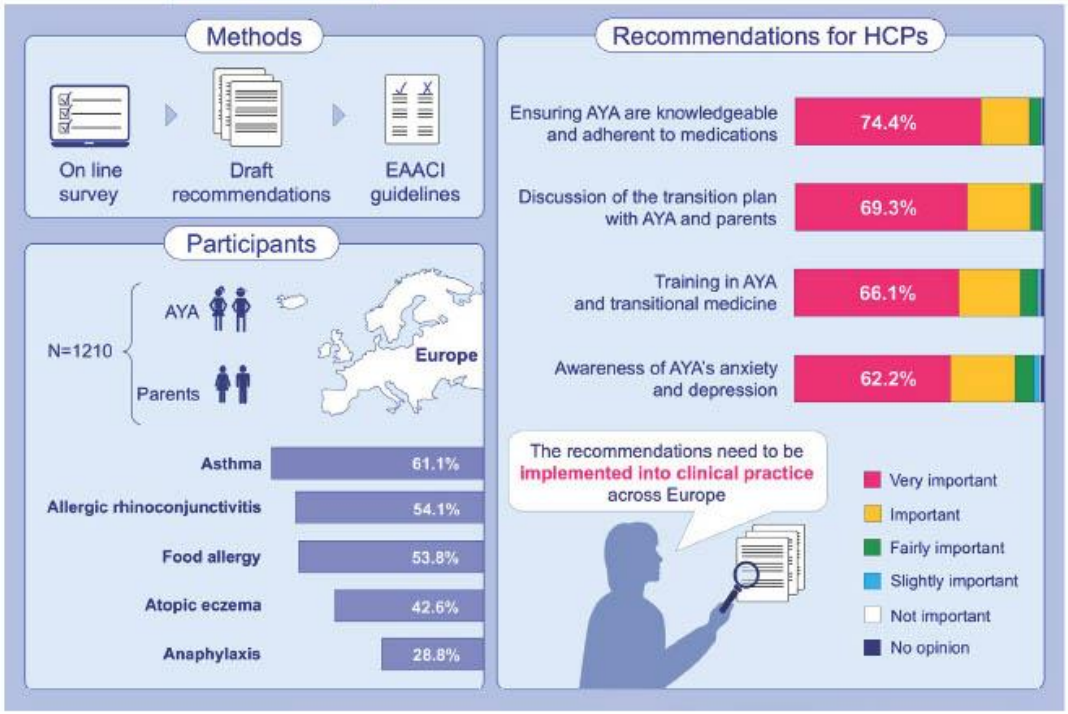

FIGURE 4 Summary of the feedback on draft recommendations of EAACI Guideline on the effective transition of adolescents and young adults with allergy and/or asthma. AYA, adolescents and young adults; HCP, healthcare professionals

questions confirmed the value of these recommendations and provided additional information from a patient perspective. Next steps should include implementation of recommendations into clinical practice taking into account differences between European countries in how transition may be organized.

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CONFLICT OF INTEREST

GR and RK report research funding from Asthma UK and National Institutes of Health Research into the challenge associated with asthma during adolescents. FT reports being a parent of a young adult with food allergy. None of the other authors have anything to disclose.

AUTHOR CONTRIBUTIONS

GR, EK and M.V.-O involved in survey concept and design. EK and GR involved in statistical analysis and interpretation of data, and drafting of the original manuscript. EK, GR, CA, RCK, AG, PC, T.G-B and MHG involved in qualitative analysis. GR, M.V-O., EA, KB, RCK, PC, CA, BD, CGM, AD, CG, VH, BJ, HP, AFS, T.G-B, SSG, MHG, FT and OF reviewed and edited the manuscript. All authors provided critical review of the manuscript and approved the final version. Obtained funding, GR, M.V-O.

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SUPPORTING INFORMATION

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On-line supplement

Perceptions of adolescents and young adults with allergy and/or asthma and their parents on EAACI guideline recommendations about transitional care: A European survey.

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Online questionnaire

Making allergy, skin disease and asthma care better for young people

The European Academy of Allergy and Clinical Immunology is a medical organisation for doctors and nurses who look after people with allergy, skin disease and asthma. We are currently writing advice for doctors and nurses who look after young people.

Young people are between 11 to 25 years old. During this time they may be cared for by different doctors, nurses and other medical staff. We need to check that the advice and care we are giving to them is helpful for patients and parents.

We want to make allergy, skin disease and asthma medical care better for young people across Europe. To do this, we need to find out what you think about medical care for yourself (or for your child if you are a parent or carer). Thank you for helping by answering the questions below. Your feedback is very important.

We will use your feedback to improve the advice that we give. This should help doctors and nurses to improve their care of young people with allergy, skin disease and asthma. We will publish and present this advice at scientific meetings.

If you are a **young person aged 11 to 25 years or the parent of a young person of this age**, we would invite you to answer our questionnaire.

There are 24 questions, we expect it to take you about 15-20 minutes.

Part one – these questions are about you, your answers will help us to know who has answered this survey

1. Are you a young person or a parent of young person with allergy, skin disease or asthma? *(choose one)*
   - Young person
   - Parent
2. Are you male or female? *(choose one)*
   - Male
   - Female
3. How old are you? *(years)*
4. What type of allergy or asthma or skin disease do you/your child have? *(choose all that apply)*
   - Asthma
   - Food allergy

4

- Urticaria (itchy rash, sometimes red and with bumps)
- Allergic rhinitis and conjunctivitis (runny or itchy nose or eyes sometimes called hay fever)
- Atopic dermatitis or atopic eczema
- Anaphylaxis in the past (serious or severe allergic reaction with possible breathing or consciousness issues)
- Allergic reaction to a medicine from the doctor, hospital or pharmacy
- Allergy to stings from wasps or bees

5. Which country are you from? *(choose one)*

Part two – these questions are about the draft advice

In this part we are asking you to rate each of the recommendations that we have drafted for doctors and nurses. Please think about how important each recommendation is for you / your child.

Please score each recommendation from 'non important' to 'very important'. You are also welcome to provide some comments about each recommendation.

General recommendations

6. Young people should start to learn how to manage their own asthma, allergies and skin disease when they are about 11-13 years old.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

7. It is important to think about:

- Making sure that clinics have a plan/special document about how to care for young people as they grow up.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

- Telling the young person and their parents or carers about how the plan will work and how it will change as they grow up.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

- Using a checklist to find out when the young person is ready to take more responsibilities for their own asthma, allergy and skin disease as they grow up.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

- Checking that the young person is able to and takes the medicines they have been given.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

- If the young person has to move across from a children's clinic to one for adults, it would be helpful for them to see both children's and adult's doctors in one clinic transiently while they get used to the change.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

- The doctors and nurses caring for young people in children's and adult clinics should have regular meetings to discuss their care.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

8. Doctors and nurses could use web-based and other mobile technologies such as texts or skype to communicate with the young person.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

9. It may be helpful for doctors and nurses to talk to young people about how their asthma, allergies and skin disease may affect their social life (e.g. when being with friends or family), education and career plans.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

10. Doctors, nurses and other medical staff should have special training to help young people with asthma, skin symptoms and allergies.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

11. There should be regular checks of how well the clinic works to make sure it is effective and helpful for young people.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

Treatment of allergy, skin disease and asthma

12. The doctors and nurses should try to make the young people's treatment easy to follow.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

13. Phone reminders, apps and other methods may be useful to help young people to remember their treatment and take more responsibility for looking after their asthma, skin disease and allergies.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

Self-management of allergy, skin disease and asthma

14. A personal action plan covering what to do would help young people manage their asthma, skin disease or allergies.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

15. It would be helpful during the hospital visit to focus on issues and ways to manage asthma, skin disease and allergies where the young person is less confident.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

16. Young people and their family might want guidance from doctors and nurses on how to manage their asthma, skin disease or allergies when the young person is at social events (e.g. sports, celebration, holidays).

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

17. Young people could learn from other contemporaries with asthma, skin disease and allergies about how to manage their life.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

18. Doctors or nurses should have conversations with teenagers designed to strengthen their motivation and commitment to improve their asthma management.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

Psychological issues and help

19. Doctors and nurses should look out for young people who feel anxious or depressed as these may affect their asthma, skin disease and allergies.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

20. Doctors and nurses should find out if young people have experienced stressful events (such as parents' divorce or bullying) which may affect their asthma, skin disease and allergies.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

21. A psychologist may be able to help young people to manage their asthma, skin disease and allergies better.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

Support from family, friends and others

22. Families should be encouraged to support young people as they start to manage their own asthma, skin disease and allergies.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

23. Young people should be encouraged to let their friends know about their asthma, skin disease and allergies and how they can help in an emergency.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

24. Clinics should recommend reliable websites and other useful sources of information about asthma, skin disease and allergies to young people.

Not important	Slightly important	Fairly important	Important	Very important	No opinion

Please provide your comment (optional)

Thank you for helping by answering the questions. Your feedback is very important. We will use it to make allergy, skin disease and asthma medical care better for young people across Europe.

Doctors Kate Khaleva, Graham Roberts and Marta Vazquez-Ortiz on behalf of the European Academy of Allergy and Clinical Immunology Adolescent and Young Adult Task force.

Table S1. Agreement on recommendations by country

Recommendation	Italy N=251	Portugal N=206	Denmark N=54	France N=189	Russia N=186	Spain N=71	UK N=103	P value
Generic advice								
1. Young people should start to learn how to manage their own asthma, allergies and skin disease when they are about 11-13 years old.	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	5 (5,5)	0.212
2. It is important to think about:								
• Making sure that the clinics have a plan/special document about how to care for young people as they grow up.	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	4 (3,5)	5 (4,5)	5 (5,5)	**0.006**
• Telling the young person and their parents or carers about how the plan will work and how it will change as they grow up.	5 (5,5)	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	5 (5,5)	0.388
• Using a checklist to find out when the young person is ready to take more responsibilities for their own asthma, allergy and skin disease as they grow up.	5 (4,5)	4.5 (4,5)	4 (4,5)	5 (4,5)	4 (3,5)	5 (4,5)	5 (4,5)	**0.036**
• Checking that the young person is able to and takes the medicines they have been given.	5 (5,5)	5 (5,5)	5 (5,5)	5 (5,5)	5 (4,5)	5 (5,5)	5 (5,5)	**0.053**
• If the young person has to move across from a children's clinic to one for adults, it would be helpful for them to see children's and adult's doctor in one clinic transiently as they get used to the change.	4 (3,5)	4 (4,5)	4 (3,5)	4 (3,5)	4 (3,4)	4 (3,5)	4 (3,5)	**0.036**
• The doctors and nurses caring for young people in children's and adult clinics should have regular meetings to discuss their care.	5 (4,5)	4 (4,5)	4 (4,5)	5 (4,5)	4 (3,4)	4 (3,5)	4 (4,5)	**0.000**
3. Doctors and nurses could use web-based and other mobile technologies such as texts or skype to communicate with the young person.	4 (4,5)	4 (4,5)	4 (3,5)	4 (3,5)	4 (3,5)	4 (3,5)	4 (3,5)	0.856
4. It may be helpful for doctors and nurses to talk to young people about how their asthma, allergies and skin disease may affect their social life (e.g. when being with friends or family), education and career plans.	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	4 (4,5)	5 (4,5)	5 (4,5)	**0.008**
5. Doctors, nurses and other medical staff should have special training to help young people with asthma, skin symptoms and allergies.	5 (4,5)	5 (4,75;5)	4 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	**0.000**
6. There should be regular checks of how well the clinic works to make sure it is effective and helpful for young people.	5 (4,5)	5 (4,5)	4 (4,5)	4 (4,5)	4 (4,5)	5 (4,5)	4 (4,5)	0.157
Treatment of allergy, skin disease and asthma								
7. The doctors and nurses should try to make the young people's treatment easy to follow.	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	4 (3,5)	5 (4,5)	5 (4,5)	**0.000**
8. Phone reminders, apps and other methods may be useful to help young people to remember their treatment and take more responsibility for looking after their asthma, skin disease and allergies.	4 (4,5)	5 (4,5)	4 (4,5)	4 (4,5)	4 (3,5)	4.5 (4,5)	4 (4,5)	0.917
Self-management of allergy, skin disease and asthma								
9. A personal action plan covering what to do would help young people manage their asthma, skin disease or allergies.	5 (4,5)	5 (4,5)	4 (4,5)	5 (4,5)	4 (4,5)	5 (4,5)	5 (4,5)	0.075

Recommendation	Italy N=251	Portugal N=206	Denmark N=54	France N=189	Russia N=186	Spain N=71	UK N=103	P value
10. It would be helpful during the hospital visit to focus on issues and ways to manage asthma, skin disease and allergies where the young person is less confident.	5 (4,5)	5 (4,5)	4 (4,5)	4.5(4,5)	4 (3,5)	4 (4,5)	5 (4,5)	0.497
11. Young people and their family might want guidance from doctors and nurses on how to manage their asthma, skin disease or allergies when the young person is at social events (e.g. sports, celebration, holidays).	5 (4,5)	5 (4,5)	4.5 (3,5)	4 (3,5)	4 (3,5)	4 (4,5)	5 (4,5)	0.424
12. Young people could learn from other young people with asthma, skin disease and allergies about how to manage their life.	4 (4,5)	4 (4,5)	4 (4,5)	5 (4,5)	4 (3,5)	4 (4,5)	4 (4,5)	**0.046**
13. Doctors or nurses should have conversations with young people designed to strengthen their motivation and commitment to improve their asthma management.	5 (4,5)	5 (4,5)	4 (4,5)	4 (4,5)	4 (4,5)	4 (4,5)	5 (4,5)	0.469
Psychological issues and help								
14. Doctors and nurses should look out for young people who feel anxious or depressed as these may affect their asthma, skin disease and allergies.	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	5 (5,5)	0.683
15. Doctors and nurses should find out if young people have experienced stressful events (such as parents' divorce or bullying) which may affect their asthma, skin disease and allergies.	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	4 (3,5)	4 (4,5)	4 (3,5)	0.083
16. A psychologist may be able to help young people to manage their asthma, skin disease and allergies better.	4 (4,5)	4 (4,5)	4 (3,5)	4 (4,5)	4 (3,5)	4 (3,5)	5 (4,5)	0.579
Support from family, friends and others								
17. Families should be encouraged to support young people as they start to manage their own asthma, skin disease and allergies.	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	4 (4,5)	5 (5,5)	0.320
18. Young people should be encouraged to let their friends know about their asthma, skin disease and allergies and how they can help in an emergency.	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	4 (3,5)	5 (4,5)	5 (5,5)	0.144
19. Clinics should recommend reliable websites and other useful sources of information about asthma, skin disease and allergies to young people.	5 (4,5)	4 (4,5)	4 (3,5)	4 (3,5)	4 (4,5)	5 (4,5)	5 (4,5)	**0.010**

Figures are median (25th centile, 75th centile). Potential responses were 1 "Not important," 2 "Slightly Important," 3 Fairly important", 4 "Important," and 5 "Very Important," plus a "No opinion" option was available. UK, United Kingdom. P-values represent a Kruskal Wallis test was used to compare responses across different countries.

I. Generic section.

Table S2. Feedback on recommendation 1: young people should start to learn how to manage their own asthma, allergies and skin disease when they are about 11-13.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
It promotes confidence, autonomy, independence	++++	++	+++	Perception that responsibility for education lies on both parents and HCPs	++	-	++	Need to start learning about self-management earlier	++++	++	++++
It promotes increased awareness of the risks, symptoms and treatment. It may reduce the risk and need for treatment	+++	++	++	Only under supervision. AYA need reminders and help	+	+	+	Need to start learning about self-management later	+	+	+
This is needed as there is lack of knowledge and support from school or others	+	+	+	Timing depends on the AYA	+	-	+				
This is the best age	+	+	+	Should be a balance between safety and autonomy in this age group	+	+	+				
It may increase adherence to treatment and get them into a habit	+	-	+	Should start learning about self-management from diagnosis	+	+	+				

AYA: adolescents and young adults. HCPs: healthcare professionals. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total number of comments= 178; AYA=55 (30.9%); parent=123 (69.1%). Total number of supportive comments =119; AYA=50 (42%), parents=69 (58%). Total number of conditionally supportive comments =33; AYA =3 (9%), parents =30 (91%). Total number of non-supportive comments =89; AYA =23 (25.8%), parents =66 (74.2%). Overall Total =241; Supportive % of Overall Total = 49.4 %.

Table S3. Feedback on recommendation 3: doctors and nurses could use web-based and other mobile technologies such as texts or skype to communicate with the young people.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
Promotes good communication and supports management	++++	++	+++	Only as complementary to face to face care	+	+	+	Face to face care is preferable	+	+	+
More meaningful for AYA	+++	++	+++	Only as a reminder of medication, expiry dates and appointments	+	+	+	This may be a burden on healthcare resources	+	+	+
Promotes self-efficacy and empowerment	+++	++	++	Only for low risk groups and if shared with parents	+	+	+	Would undermine AYA need to take responsibility for own care	+	+	+

AYA: adolescents and young adults. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total number of comments= 119; AYA= 41(34.5%), parents=78 (65.5%). Total number of supportive comments =139; AYA=51 (37%), parents=88 (63%). Total number of conditionally supportive comments =17; AYA =6 (35%), parents = 11 (65%). Total number of non-supportive comments =14; AYA =7 (50%), parents =7 (50%). Overall Total =170; Supportive % of Overall Total = 82%.

Table S4. Feedback on recommendation 4: it may be helpful for doctors and nurses to talk to young people about how their asthma, allergies and skin disease may affect their social life (e.g. when being with friends or family), education and career plans.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
HCS should be encouraged to introduce sensitive topics into the clinic discussion	++++	++	+++	Engage with community or school and peers to discuss and support living with and managing AYA allergies and asthma	++	+	++	Task for parents	+	+	+
Discussions about how their symptoms may affect day to day life may improve adherence and how to manage future emergencies	++	+	++	HCP mediation between AYA and family, e.g tackling overprotective regimes or AYA adherence	+	+	+	Not necessary	+	-	+
Psychological support may be needed to reduce anxiety or support development	++	-	++	Promote positive self-image with eczema or appearance	++	+	+				
Need for additional help or resources	++	+	+	Future plans, e.g occupational considerations - need to be discussed openly but also positively	+	+	+				
Increased risks with alcohol or smoking	+	+	+								
Food allergy specific, eg unexpected allergens in cosmetics or drinks	+	+	+								
How to manage allergies and asthma around peers	+	+	-								

AYA: adolescents and young adults. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total number of comments = 113: AYA= 32 (28%); parents = 81 (71%). Total number of supportive comments = 121; AYA=35 (28.9%), parents=86(71.1%). Total number of conditionally supportive comments =58; AYA =19 (32.8%), parents =39 (67.2%). Total number of non-supportive comments =4; AYA= 1(25%), parents =3 (75%). Overall Total =183; Supportive % of Overall Total = 66%.

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Table S5. Feedback on recommendation 5: doctors, nurses and other medical staff should have special training to help young people with asthma, skin symptoms and allergies.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
Need or importance for awareness of the risk/signs and treatment (HCP & patients)	++	+	++	Need to take into account the specific characteristics due to age or adolescence	+	+	+				
Perceived lack of input, empathy or knowledge from HCP (especially emergency & GP) or caregivers	+++	+	++	The importance of peer-led training	+	-	+				
Develop mandatory, essential and useful recommendation	++	+	++	Need for financial assistance (patients, HCP)	+	+	+				
Need for regular education/ training of HCP, caregivers and patients	++	+	+	Responsibility of transition lies with parents and HCP	+	-	+				
Provide psychological and psychosocial guidance for patients, family and HCP	+	+	+								
Especially important for severe asthma, allergy and emergencies	+	+	+								
Need for an integral and optimum approach and management (HCP, caregivers, school)	+	+	+								

AYA: adolescents and young adults, GP: general practitioner, HCPs: healthcare professionals. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total number of comments = 85: AYA= 23 (27%); parents= 62 (73%). Total number of supportive comments =105; AYA=31(29.5%), parents=74(70.5%). Total number of conditionally supportive comments =11; AYA=2 (18.2%), parents=9(81.8%). Total number of non-supportive comments =0; AYA =0 (0%), parents =0 (0%). Overall Total =116; Supportive % of Overall Total =90.5%.

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Table S6. Feedback on recommendation 6: there should be regular checks of how well the clinic works to make sure it is effective and helpful for young people.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
Centres must be evaluated to be sure of their effectiveness and efficiency in supporting AYA to self-manage (also to be evaluated by patients)	++	+	++	Need to use specific guidelines, training and meetings	+	-	+	Lack of confidence and further information is requested	+	+	+
Helps to improve	+	+	+	Responsibility lies with HCP	+	-	+				
Applicable to all carers	+	+	+	Need to improve access to the best specialists	+	+	+				
For patient more responsibility	+	-	+								

AYA: adolescents and young adults, HCP: healthcare professionals. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total number of comments = 43: AYA= 10 (23.3%); parents= 33 (76.7%). Total number of supportive comments =34; AYA=13 (38.2%), parents=21 (61.8%). Total number of conditionally supportive comments =12; AYA =1 (8.3%), parents = 11 (91.7%). Total number of non-supportive comments =10; AYA =1 (10%), parents =9 (90%). Overall Total =56; Supportive % of Overall Total =60.7%.

II. Adherence section.

Table S7. Feedback on recommendation 7: the doctors and nurses should try to make the young people's treatment easy to follow.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
Increase adherence and effectiveness	++	+	++	Only if individualised (depends on age and needs)	+	+	+				
Lower anxiety and increase self-efficacy and empowerment	++	+	+	Only if effective	+	+	+				
Treatment already simple	+	+	+	Only if backed up by HCP or counselling	+	-	+				

AYA: adolescents and young adults; HCP: healthcare professionals. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total number of comments = 61: AYA= 20 (32.8%); parents= 41 (67.2%). Total number of supportive comments =37; AYA=14 (38%), parents=23 (62%). Total number of conditionally supportive comments =23; AYA=7 (30%), parents= 16 (70%). Total number of non-supportive comments =0; AYA =0 (0%), parents =0 (0%). Overall Total =60; Supportive % of Overall Total =61.7%.

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Table S8. Feedback on recommendation 8: phone reminders, apps and other methods may be useful to help young people to remember their treatment and take more responsibility for looking after their asthma, skin disease and allergies.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
Promotes good communication and accurate guidance for management	++	++	++	Only as complementary to face to face care and as a reminder of medication, expiry dates and appointments	+	-	+	Would undermine AYA need to take responsibility for own care	++	+	+
More meaningful for teens	++	++	++	Only if practical, educational and interactive	+	+	-	Intrusive	+	+	+
Promotes self-efficacy and empowerment	++	+	+	Only if secure with parent access	+	-	+	In person face to face care is preferable	+	+	+

AYA: adolescents and young adults. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total number of comments =77: AYA =29 (37.7%); parents= 48 (62.3%). Total number of supportive comments =66; AYA=31 (47%), parents=35 (53%). Total number of conditionally supportive comments =11; AYA =3 (37%), parents =8 (73%). Total number of non-supportive comments =18; AYA =6 (33%), parents =12 (67%). Overall Total =95; Supportive % of Overall Total =69.5%.

III. Self-management section.

Table S9. Feedback on recommendation 9: a personal action plan covering what to do would help young people manage their asthma, skin disease or allergies.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
Action plan needs to be shared with peers, schools and others	+	+	+	HCP should develop an action plan with AYA that is individualised and appropriate	++	+	++	Not needed or required	+	+	+
Action plans useful for adherence	+	+	+	Must be clear	+	-	+	Not sure that this is required	+	-	+
Single action plan important for AYA with multiple atopic manifestations	+	-	+	Action plan needs to be supported by information about the condition(s)	+	-	+				
Help rapid treatment	+	+	-	Asthma plans but not other atopic conditions	+	+	-				
				Action plan should be developed before entering adolescence	+	-	+				
				Should be multidisciplinary	+	-	+				

AYA: adolescents and young adults; HCP: healthcare professionals. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total number of comments= 45: AYA = 12 (27%), parents = 33 (73%). Total number of supportive comments =13; AYA=3 (23%), parents=10 (77%). Total number of conditionally supportive comments =39; AYA=7 (17.9%), parents = 32 (82.1%). Total number of non-supportive comments =7; AYA =2 (28.6%), parents =5 (71.4%). Overall Total =59; Supportive % of Overall Total = 22%.

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Table S10. Feedback on recommendation 10: it would be helpful during the hospital visit to focus on issues and ways to manage asthma, skin disease and allergies where the young person is less confident.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
This will promote confidence	+	+	+	This support should be personalised	+	+	+	Not clear	+	+	+
Support is needed for related atopic conditions at the clinic	+	+	-	It should assess treatment	+	+	+	All aspects need to be covered	+	-	+
				It should address anxiety and psychological issues	+	+	+				
				This can address particular fears, eg use of AAI	+	-	+				
				HCP and AYA direct dialogue	+	-	+				
				Need for more information	+	-	+				
				It should highlight risks	+	+	-				

AAI: adrenaline autoinjector, AYA: adolescents and young adults, HCP: healthcare professionals. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total number of comments = 46: AYA = 13 (28%); parents = 33 (72%). Total number of supportive comments =11; AYA=4 (36.4%), parents=7 (63.6%). Total number of conditionally supportive comments =33; AYA=9 (27.3%), parents =24 (72.7%). Total number of non-supportive comments =4; AYA =2 (50%), parents =2 (50%). Overall Total =48; Supportive % of Overall Total =22.9%.

Table S11. Feedback on recommendation 11: young people and their family might want some help from doctors and nurses how to manage their asthma, skin disease or allergies when the young person is at social events (eg sports, celebration, holidays).

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
Would welcome such help	+++	++	++	Would value guidance, e.g. school trips, overseas	+	+	+	Recommendation not understood	++	+	++
				The role of support groups and charities	+	-	+	Would be embarrassing	+	+	-
				Asthma and allergy peer group desirable	+	+	+	Not necessary	+	+	+
				Need to involve family and friends	+	+	+				
				Advice needs to be event specific, e.g. sport, university	+	-	+				
				Would prefer to meet older people who live with these conditions	+	+	-				

AYA: adolescents and young adults. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total number of comments = 70; AYA= 24 (34%), parents = 46 (66%). Total number of supportive comments =39; AYA=14 (35.9%), parents=25 (64.1%). Total number of conditionally supportive comments =26; AYA =6 (23.1%), parents =20 (76.9%). Total number of non-supportive comments =18; AYA =5 (27.8%), parents =13 (72.2%). Overall Total =83; Supportive % of Overall Total =47%.

Table S12. Feedback on recommendation 12: young people could learn from other young people with asthma, skin disease and allergies about how to manage their life.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
More meaningful for teens with emotional support and normalisation	+++	+	+++	Only if overseen by HCP	+	+	+	Would undermine AYA need to take responsibility for own care	+	-	+
Promotes self-efficacy, empowerment, and autonomy	++	+	++	Only if individualised	+	+	+	AYA not competent	+	+	+
Practical help, advice and support	++	+	++	With support group	+	-	+	In person face to face care is preferable	+	-	+

AYA: adolescents and young adults, HCP: healthcare professionals. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total number of comments=87: AYA= 21 (24.1%); parents= 66 (75.9%). Total number of supportive comments =89; AYA=24 (27%), parents=64 (72%). Total number of conditionally supportive comments =16; AYA=3 (19%), parents =13 (81%). Total number of non-supportive comments =6; AYA =1 (17%), parents =5 (83%). Overall Total =111; Supportive % of Overall Total =80 %.

Table S13. Feedback on recommendation 13: doctors or nurses should have conversations with teenagers designed to strengthen their motivation and commitment to improve their asthma management.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
Communication is essential for self-confidence and improved care	++	+	+	Do not need to force the AYA, should only be done in agreement	+	+	+				
This will reinforce good adherence, self-management, involvement in social activities	++	+	+	Peer-group to talk about their experiences	+	+	+				
It is dangerous for AYA if they are not prepared to be independent. Needs to be done for risk reduction	+	+	+	Need for psychological support	+	-	+				
It will ensure ongoing adherence even when symptoms-free	+	+	+	Only if needed	+	-	+				
				With the help from family	+	+	-				
				Need for asthma and allergy schools	+	-	+				
				Needs to be done well otherwise can have a deleterious effect	+	+	-				
				Need time for it during the consultations	+	-	+				

AYA: adolescents and young adults. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total number of comments= 42: AYA= 12 (28.6%); parents= 30 (71.4%). Total number of supportive comments =37; AYA= 14 (37.8%), parents=23 (62.2%). Total number of conditionally supportive comments =17; AYA =4 (23.5%), parents =13 (76.5%). Total number of non-supportive comments =0; AYA =0(0%), parents =0 (0%). Overall Total =54; Supportive % of Overall Total =68.5%.

IV. Psychology section.

Table S14. Feedback on recommendation 14: doctors and nurses should look out for young people who feel anxious or depressed as these may affect their asthma, skin disease and allergies.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
Prevention: minimise negative outcomes including isolation, bullying, depression. anxiety, death, low confidence, exacerbations or refusal of treatment	+++	+	+++	Need psychological support for this	++	+	+				
This is important	+++	+	++	With involvement and support of the whole family	+	+	+				
Need to raise awareness of this in AYA	+	+	+	HCP need training in this area	+	+	+				
This area is often ignored or undervalued	+	+	+	Need for additional support, e.g. web chats, workshops	+	-	+				
Particularly important in adolescence	+	-	+	Need to recognise different contributing factors, e.g. autism	+	-	+				
Difficult to open up about fears	+	+	+	Having a consultation without parents	+	+	-				
Needs more time in the consultation for this	+	-	+								

AYA: adolescents and young adults, HCP: healthcare professionals. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++).Total number of comments= 79: AYA=18 (22.8%); parents= 61 (77.2%). Total number of supportive comments =90; AYA=25 (27.8%), parents=65 (72.2%). Total number of conditionally supportive comments =28; AYA =7 (25%), parents =21 (75%). Total number of non-supportive comments = 0; AYA =0 (0%), parents =0 (0%). Overall Total =118; Supportive % of Overall Total =76.3%.

Table S15. Feedback on recommendation 15: doctors and nurses should find out if young people have experienced stressful events (such as parents' divorce or bullying) which may affect their asthma, skin disease and allergies.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
Mention of possible stress factors	++	+	++	Involve psychological support or other	+	+	+	Not part of the allergy consultation	+	+	+
Stress can impact on asthma, allergy or eczema	++	+	+	Information should be acted on	+	-	+	Not understood	+	-	+
The impact of bullying needs to be addressed	+	+	+	Important to talk to the AYA and the parent alone	+	-	+				
School may be a source of anxiety	+	-	+	Important to address feelings post anaphylactic reactions	+	-	+				
Important to ask and look for causes of stress	+	-	+	Ask compassionately	+	-	+				

AYA: adolescents and young adults. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total number of comments = 54: AYA= 13 (24%); parents = 41 (76%). Total number of supportive comments =43; AYA=9 (20.9%), parents=34 (79.1%). Total number of conditionally supportive comments =16; AYA =2 (12.5%), parents =14 (87.5%). Total number of non-supportive comments =7; AYA =4 (57.1%), parents =3 (42.9%). Overall Total =66; Supportive % of Overall Total =65.1 %.

Table S16. Feedback on recommendation 16: a psychologist may be able to help young people to manage their asthma, skin disease and allergies better.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
Important to manage anxiety, stress, depression, improve self-confidence and treatment efficacy	+++	+	+++	Dependent on AYA's mental health or wishes	++	+	++	No need	+	+	+
Helpful when managing allergies whilst with peers, ie how to live with allergy	+	+	+	Need psychologists trained in allergy	+	+	+	Stigma associated with seeing a psychologist	+	+	+
Should be offered to parents too	+	-	+	Should be easy to access and available in all clinics	+	-	+				
Need for allergy and asthma schools or support groups	+	-	+	Needed at certain times in life	+	-	+				
To reduce family conflict	+	-	+	Need to see AYA on their own	+	+	-				
				Only complimentary to medical support	+	-	+				

AYA: adolescents and young adults. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total number of comments=69; AYA=12 (17.4%); parents=57 (82.6%). Total number of supportive comments =50; AYA=9 (18%), parents=41 (82%). Total number of conditionally supportive comments =33; AYA =5 (15.1%), parents =28 (84.9%). Total number of non-supportive comments =7; AYA =4 (57.1%), parents =3 (42.9%). Overall Total =90; Supportive % of Overall Total =55.5%.

V. Support section.

Table S17. Feedback on recommendation 17: families should be encouraged to support young people as they start to manage their own asthma, skin disease and allergies.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
Need for confidence, autonomy or independence	++	+	+	Dependent on the parents' ability; need to support parents and families	++	+	++	Risks associated to autonomy	+	+	+
Responsibility perceived to lie with parents and families	++	+	+	Balance between autonomy and supervision	++	+	+	Responsibility lies on social workers	+	+	-
To increase adherence to treatment	+	+	+	Gradual transition depending on the motivation of the child	+	-	+				

AYA: adolescents and young adults. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total comments = 49: AYA= 11 (22.4%); parents= 38 (77.6%). Total number of supportive comments =28; AYA=9 (32.2%), parents=19 (67.8%). Total number of conditionally supportive comments =34; AYA =5 (14.7%), parents =29 (85.3%). Total number of non-supportive comments =5; AYA =2 (50%), parents =3 (60%). Overall Total =67; Supportive % of Overall Total =41.8%.

Table S18. Feedback on recommendation 18: young people should be encouraged to let their friends know about their asthma, skin disease and allergies and how they can help in an emergency.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
Support from contacts (eg friends, schoolmates, sports mates, teachers) is very important for AYA	+++	++	+++	Need to reduce risk for feeling different, experiencing, embarrassment or bullying	++	+	++	Challenging topic for AYA; AYA do not like talking about it	++	+	++
Need for awareness of the risks, signs, prevention and treatment (eg friends, school, contacts)	+++	++	++	Need help to do this; need for assertiveness training	+	+	+	It may be not useful, eg first aiders scared of using AAI, being sued, insufficient skills	+	-	+
Need to help especially in emergency situations when need AAI or inhalers	++	+	++	Need to be selective, eg just close friends	+	-	+				
				It depends on AYA's opinion	+	-	+				
				It deepens on the age	+	-	+				

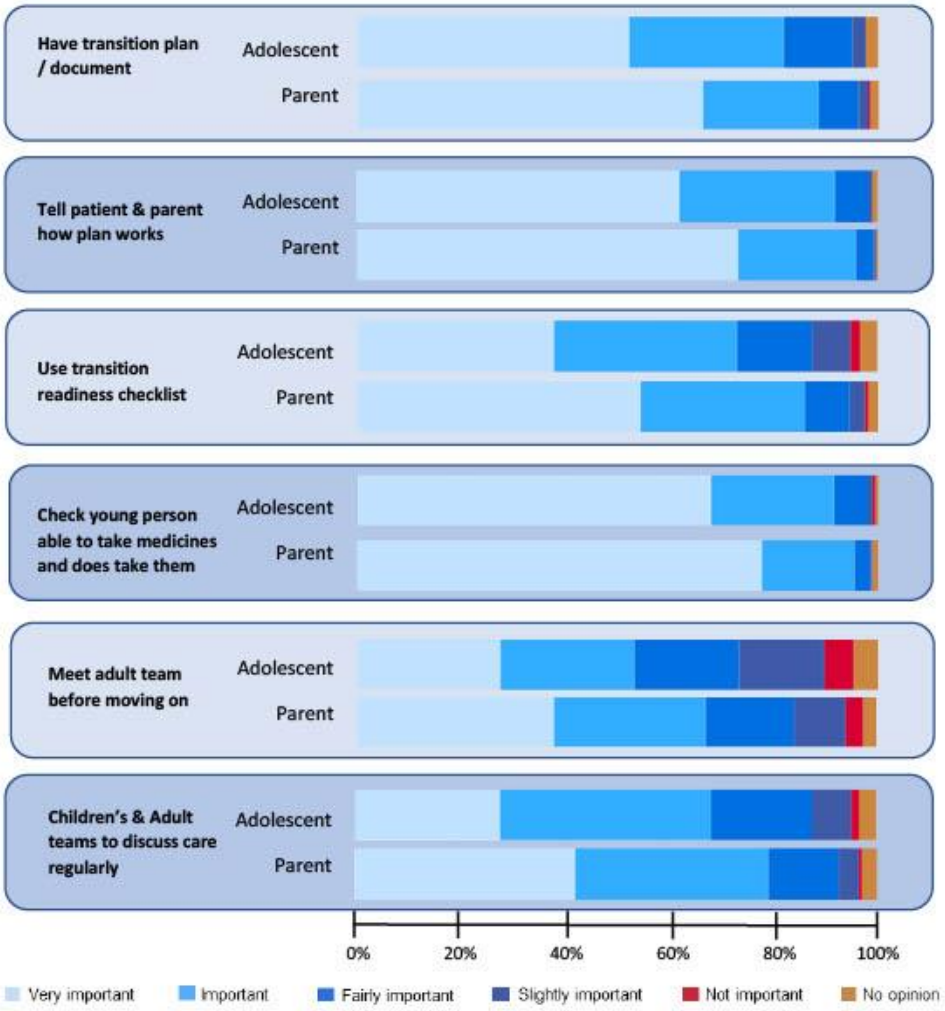
AAI: adrenaline autoinjector. AYA: adolescents and young adults. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total comments = 100: AYA= 24 (24%); parents= 76 (76%). Total number of supportive comments =94; AYA=31 (32.9%), parents=63 (67.1%). Total number of conditionally supportive comments =41; AYA =5 (12.2%), parents = 36 (87.8%). Total number of non-supportive comments =22; AYA =1 (4.5%), parents =21 (95.5%). Overall Total =157; Supportive % of Overall Total = 59.8%.

Table S19. Feedback on recommendation 19: clinics should recommend reliable websites and other useful sources of information about asthma, skin disease and allergies to young people.

Supportive themes	Number of comments			Conditionally supportive themes	Number of comments			Non-supportive themes	Number of comments		
	Total	AYA	Parents		Total	AYA	Parents		Total	AYA	Parents
Need for concise, clear, updated and accurate	++	+	++	Need to share information and talk with their peers, friends and family	+	+	+	It is not clear	+	+	+
Need for further and attractive information with new technologies; knowledge is power	++	+	+	Need for talking directly with HCP to understand information	+	-	+	Responsibility of information lies on AYA	+	-	+
Responsibility of providing this type of further information lies with the HCP	+	+	+					Too much internet	+	-	+
Lack of this information from HCP	+	-	+								

AYA: adolescents and young adults, HCP: healthcare professionals. Pluses are based on the number of comments: 0 (-); 1-10 (+); 11-29 (++); 30-49 (+++); ≥50 (++++). Total comments = 39: AYA= 8 (20.5%); parents= 31 (79.5%). Total number of supportive comments =36; AYA=8 (22.2%), parents=28 (77.8%). Total number of conditionally supportive comments =7; AYA =1 (14.3%), parents =6 (85.7%). Total number of non-supportive comments =6; AYA =1 (16.6 %), parents =5 (83.4%). Overall Total =49; Supportive % of Overall Total =73.5%.

Figure S1. Summary of feedback on additional generic recommendations



A3. Chapter 3. Publication 2.

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My contribution: G Roberts and myself: study concept and design.

The first four points were conducted in duplicate with A. Rattu (PhD student, University of Southampton) and published as part of the systematic review underpinning COMSA development: 1) developed search strategies, performed database searches, screening of records, performed data extraction; 2) developed and analysed results of a modified Delphi exercise within four stakeholder groups; 3) appraised development, validity, and reliability of selected outcome measures using COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN); 4) provided training to study participants including patients about study methodology.

To ensure patient-centered approach, I conducted monthly calls with Respiratory Patient Working Group (PWG) about study methodology. Then, together with PWG I developed, disseminated and analysed a survey including qualitative analysis in duplicate with A. Rattu and quantitative analysis by myself. For the narrative review, I developed search strategies, conducted titles and abstracts screening in duplicate with A. Rattu.

Prior to the consensus meeting, I coordinated drop-in meetings for stakeholders. I then prepared an on-line voting forms and led series of paediatric and adult consensus meetings to discuss the evidence from the systematic review, a pan-European survey. I utilized the GRADE Evidence to Decision framework to guide the decision-making, orchestrated the voting process and analysed the results. Lastly, I drafted the original manuscript.

EUROPEAN RESPIRATORY JOURNAL
REVIEW
E. KHALEVA ET AL.

Development of Core Outcome Measures sets for paediatric and adult Severe Asthma (COMSA)

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Shareable abstract (@ERSpublications)
A European multi-stakeholder working group has reached a consensus on Core Outcome Measures sets for paediatric and adult Severe Asthma (COMSA). These should inform future clinical trials and enhance comparability of findings. https://bit.ly/3yO2gB2

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Abstract

Background Effectiveness studies with biological therapies for asthma lack standardised outcome measures. The COMSA (Core Outcome Measures sets for paediatric and adult Severe Asthma) Working Group sought to develop Core Outcome Measures (COM) sets to facilitate better synthesis of data and appraisal of biologics in paediatric and adult asthma clinical studies.

Methods COMSA utilised a multi-stakeholder consensus process among patients with severe asthma, adult and paediatric clinicians, pharmaceutical representatives, and health regulators from across Europe. Evidence included a systematic review of development, validity and reliability of selected outcome measures plus a narrative review and a pan-European survey to better understand patients' and carers' views about outcome measures. It was discussed using a modified GRADE (Grading of Recommendations Assessment, Development and Evaluation) Evidence to Decision framework. Anonymous voting was conducted using predefined consensus criteria.

Results Both adult and paediatric COM sets include forced expiratory volume in 1 s (FEV_1) as z-scores, annual frequency of severe exacerbations and maintenance oral corticosteroid use. Additionally, the paediatric COM set includes the Paediatric Asthma Quality of Life Questionnaire and Asthma Control Test or Childhood Asthma Control Test, while the adult COM set includes the Severe Asthma Questionnaire and Asthma Control Questionnaire-6 (symptoms and rescue medication use reported separately).

Conclusions This patient-centred collaboration has produced two COM sets for paediatric and adult severe asthma. It is expected that they will inform the methodology of future clinical trials, enhance comparability of efficacy and effectiveness of biological therapies, and help assess their socioeconomic value. COMSA will inform definitions of non-response and response to biological therapy for severe asthma.

Introduction

Severe asthma is defined by the European Respiratory Society/American Thoracic Society (ERS/ATS) as asthma which requires treatment with high-dose inhaled corticosteroids and a second controller and/or systemic corticosteroids to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy [1]. Severe asthma affects ~5–10% of patients with asthma [1]; however, there is variability in the prevalence estimates in children and adults [2]. It is associated with a significant impact on quality of life (QoL) [3], treatment [4, 5] and socioeconomic burden [4, 6–8]. Many patients with severe asthma miss school [9] or are unable to maintain full-time employment [10] and some fail to respond to traditional asthma treatments.

Biological therapies for severe asthma improve individual patient outcomes [11]. A series of systematic reviews reported that biologics improve asthma control and QoL, and decrease exacerbation rates and

rescue medication use [12–14]. However, there is significant heterogeneity in which outcome measures are reported and what definitions are used in clinical trials. This makes it challenging to draw definite conclusions about the relative effectiveness of different biological agents, particularly given the paucity of head-to-head trials. Additionally, there are different eligibility criteria for initiating biologics in paediatric and adult patients [15, 16], and this makes comparisons between different trials difficult. Although validated and reliable outcomes or outcome measures for asthma have been recommended in the National Institutes of Health series [17–22], coreASTHMA [23], clinical asthma registries [24] and asthma trials [25], there is no agreement on what is the most appropriate Core Outcome Measures (COM) set for trials with biological therapies in severe asthma. A COM set is a minimum, standardised group of outcome measures that should be used and reported in all future clinical trials [26]. The development of a COM set requires a multi-step process involving all relevant stakeholders, including clinicians, patients and their families, to identify outcome measures that have suitable measurement properties, are most relevant and are feasible for use.

To address the need for a robust set of outcome measures for severe asthma, we aimed to develop pan-European consensus patient-centred COM sets for use in studies of biological therapies in paediatric and adult patients with severe asthma. Having standardised COM sets would enable improved reporting and synthesis of outcome measures and therefore reduce publication bias, allow meaningful comparisons of efficacy and effectiveness of different biological therapies, and improve policy and patient–doctor shared decision making.

Methods

The COMSA initiative is registered on the Core Outcome Measures in Effectiveness Trials (COMET) database (www.comet-initiative.org/Studies/Details/1698). The approach was adapted from the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) initiative to select outcome measurement instruments for the COM set [26] and is reported in accordance with the Core Outcome Set-STAndards for Reporting (COS-STAR) statement (supplementary table S1) [27]. Approval was gained from the Ethics Committee of the University of Southampton (Southampton, UK) (ERGO 56181). This project is part of the 3TR (Taxonomy, Treatments, Targets and Remission) Consortium (https://3tr-imi.eu) funded by the European Commission's Innovative Medicines Initiative 2.

Participants for COM sets consensus process

Four key stakeholder groups were involved.

1) Paediatric and adult patient representatives with severe asthma. These included the 3TR Respiratory Adult and Youth Patient Working Groups (PWGs) as well as patient advocacy organisations including the European Lung Foundation (ELF), European Federation of Allergy and Airways Diseases Patients' Associations (EFA), Global Allergy & Airways Patient Platform (GAAPP), and Lovexair. The ELF and EFA recruited patients and carers of patients with severe asthma from across Europe through their networks to capture a range of disease duration, unique experiences and treatments, including biological therapy. Monthly calls with the two PWGs were held throughout the project to ensure a patient-centred approach in deciding the COM set for severe asthma. At these meetings, patients and patient advocates received online training about clinical trial design, outcome selection, core outcomes, the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach and the consensus process. Minutes and training materials were shared with PWG members after each call.

2) Paediatric and adult clinicians were invited by the lead (G.R.) and senior (E.K.) investigators, and included paediatricians, allergists, respiratory clinicians, nurses, researchers and methodologists. The selected world-leading physicians had a broad range of clinical knowledge and expertise in managing patients with severe asthma on biologics. None of the participants were involved in the development of specific outcome measurement instruments.

3) Pharmaceutical industry representatives from AstraZeneca, Sanofi, Roche and Novartis who are partners in the 3TR Consortium.

4) Regulators from European medicinal products regulatory authorities (hereafter referred to as "health regulators"). The selected health regulators had a broad range of regulatory knowledge and/or were specialised in the field of paediatric and/or adult allergology and respiratory medicine.

Overview of COM set development

Paediatric (children and adolescents aged 6–17 years) and adult (≥18 years) COM sets were developed using a similar multi-stage approach to synthesise the evidence and achieve consensus (figure 1).

Stage 1: A systematic review to identify and appraise priority outcome measures for severe asthma

The detailed methods used to develop COM sets are provided in the systematic review [28]. In brief, Step 1 involved the generation of a list of "candidate" asthma outcome measures from a systematic literature search from the previous 2 years. Step 2 involved a modified two-round Delphi exercise among four stakeholder groups and a moderated web conference to select "key" outcome measures (rated as "critical" or "important" [29]). Step 3 involved a systematic literature search [28] to identify "initial" validation studies for the key outcome measures and compare against good measurement properties criteria using modified COSMIN methodology [30–32].

Stage 2: Capturing patients' and carers' views

A narrative review was undertaken by two reviewers (C.C. and C.W.) to synthesise evidence about patients' and carers' perceptions and opinions about outcome measures for severe asthma. Three bibliographic databases were searched from the year 2000. Full details are provided in the supplementary material.

A cross-sectional pan-European survey was conducted to gain insight in the perspectives of the wider patient population about outcome measures used for severe asthma. See the supplementary material for further details.

Stage 3: Multi-stakeholder consensus meetings

The aim of the consensus meetings for paediatric and adult outcome measures was to provide an opportunity to better understand views of different stakeholder groups, discuss key issues, resolve any disagreements and reach consensus on the final COM sets.

Initial meetings to reduce to priority outcome measures

The systematic review evidence, together with the results of a narrative review and a pan-European survey of patients' and carers' perceptions and preferences about outcome measures for severe asthma (supplementary material), was discussed in two initial multi-stakeholder meetings. Materials were provided 1 week before meetings. Patient-reported outcome measures (PROM) such as asthma-specific QoL, general QoL, asthma control, asthma symptoms and composite outcome measures were discussed in the first meeting followed by online voting to select eight priority PROM. Clinical and healthcare use outcome measures such as forced expiratory volume in 1 s (FEV_1), fractional exhaled nitric oxide (F_{ENO}), peak expiratory flow (PEF), FEV_1/forced vital capacity ratio, blood and/or sputum eosinophils, hospitalisations, exacerbations, adverse events, and oral corticosteroid (OCS) use were discussed at the second meeting followed by online voting to select four priority outcome measures [28]. Results were presented using the GRADE system [33].

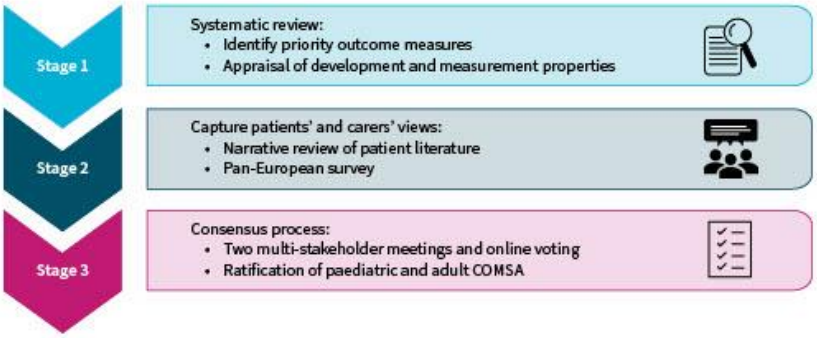

FIGURE 1 Core Outcome Measures set development process. COMSA: Core Outcome Measures for paediatric and adult Severe Asthma.

Consensus meeting to decide on COM sets

Prior to the adult and paediatric consensus meetings, all participants received the agenda, reading materials, including results of the systematic review about the development and measurement properties of priority outcome measures [28], comments from previous multi-stakeholder discussions, original copies of questionnaires, results of the pan-European survey (supplementary material) and narrative review (supplementary material) as well as data from the European Academy of Allergy and Clinical Immunology (EAACI) systematic reviews [12–14] and a systematic review of real-life studies on biological therapies [34]. All materials included summaries of the results in lay language, with an additional lay glossary of terms. Participants were invited to attend optional drop-in sessions to ask questions about materials prior to the consensus meetings.

Primary consideration was given to content validity results about relevance, comprehensiveness and comprehensibility as per COSMIN guidance on selecting core outcome measurement instruments [26] as well as patient-centred literature. During previous discussions participants highlighted that the ideal outcome measures for biological trials should also have good responsiveness, established minimal clinically important difference (MCID)/minimal important difference (MID) and be relevant to severe asthma patients. Participants were invited to share their views, refine definitions, address discrepancies across stakeholders and suggest possible combinations of outcome measures.

The online consensus meetings were held on 7 June 2021 to evaluate the evidence for adult severe asthma and on 20 July 2021 for paediatric severe asthma to ratify the final COM sets. Although these meetings were initially planned to be face-to-face with all stakeholder groups, this was changed to virtual meetings due to coronavirus disease 2019 (COVID-19) public health restrictions. Each meeting was recorded to facilitate minutes and a link was shared with those participants who were not able to attend.

COM set voting

An anonymised electronic voting process was employed after the meetings. All 3TR participants received minutes, evidence discussed at the meetings and a link to an online voting form to share their views. Along with minimal demographic information, in the first round participants were asked to select up to five and six outcome measures for paediatric and adult COM sets, respectively, and rank them in the order of importance. A free-text comment box was available to provide rationale and further arguments for inclusion or exclusion of outcome measures. Votes from clinicians, researchers, pharmaceutical representatives and health regulators were included in the "academic" group, while votes from patients and patient representatives were classified into the "patient" group. Outcome measures that scored ⩾70% of the panellist's groups' (patient or academic) votes were judged to have met consensus for inclusion based on COMET guidelines and previous patient-centred COM sets [35, 36]. Several reminders were sent to improve participation in the voting.

Results of the first round were analysed and collated into a summary of votes and comments divided by stakeholder group. Prior to the next round of voting, this summary was shared with the 3TR panel (four key stakeholder groups) who were invited to provide further comments about the group of outcome measures where consensus was not achieved (<70% agreement). Subsequently, all participants were invited to take part in Round 2 (and additionally Round 3 for the adult COM set) voting for these outcome measures. A summary of all comments as well as initial voting results and evidence with comments from the meetings were included in the invitation e-mail.

Statistical analysis

All data from the pan-European survey and online voting were analysed using SPSS version 26.0 (IBM, Armonk, NY, USA). Descriptive statistics were used to describe respondent characteristics. Medians with lower and upper quartiles are presented for continuous variables given the distribution of the data. Frequency tables with percentages are provided for categorical variables. Summary tables and figures were used to represent the results.

Results

Stage 1: A systematic review to identify and appraise priority outcome measures for severe asthma

Step 1 led to the identification of 96 candidate outcome measures. These were reduced to 55 key measures in the modified Delphi exercise (Step 2). Subsequently, following the systematic literature search and multi-stakeholder meetings, eight and nine priority outcome measures were identified for adult and paediatric populations, respectively (Step 3). The validity and reliability of the priority measures (Step 4) are discussed elsewhere [28].

Stage 2: Capturing patients' and carers' views

Narrative review

The systematic literature search found 127 papers out of which seven papers met the inclusion criteria (supplementary figure S1). Patient perspectives were extracted about the following outcome measures: PEF monitoring [37–39], hospitalisations [3, 37, 38, 40], exacerbations [41], adverse events [3, 37, 38, 40–42] and reducing OCS use [37, 38, 40–42]. Avoiding hospitalisation, decreasing OCS use and related side-effects, and reducing the number and severity of exacerbations are treatment priorities identified by patients. More details are available in the supplementary material.

A pan-European survey

A total of 201 (87%) patients and 31 (13%) parents/carers of patients with severe asthma completed the survey. Most were female (77% and 87% patients and parents/carers, respectively), had completed university education (59% and 71%, respectively) and 54% were being treated with a biological therapy (supplementary table S2).

Patients and carers, respectively, identified the following characteristics in regard to filling out questionnaires as "very important": "longer recall period, *e.g.* ⩾2 weeks" (59% and 65%), "accurate results even if it takes longer to complete" (51% and 32%), "opportunity to complete at home" (39% and 45%) and either "using a mobile app" (40% and 29%) or "using a computer" (39% and 48%) (figure 2). Responders were willing to complete a questionnaire once every month (38% and 16%) or as often as their doctor recommends (34% and 36%). It should ideally take only 6–10 min (45% and 36%) (supplementary figure S2 and supplementary table S3).

The following characteristics of lung function tests were favoured the most and rated as "very important" in the survey by patients and carers, respectively: "accuracy of the results" (83% and 65%) and "safe to complete" (67% and 59%) (supplementary figures S3 and S4, and supplementary table S4). Further results, themes and quotes can be found in supplementary figures S5 and S6, and supplementary tables S5 and S6.

When survey respondents were asked to select only five outcomes, they ranked the following as first or second most important for patients and parents/carers, respectively: "emergency hospital admissions due to

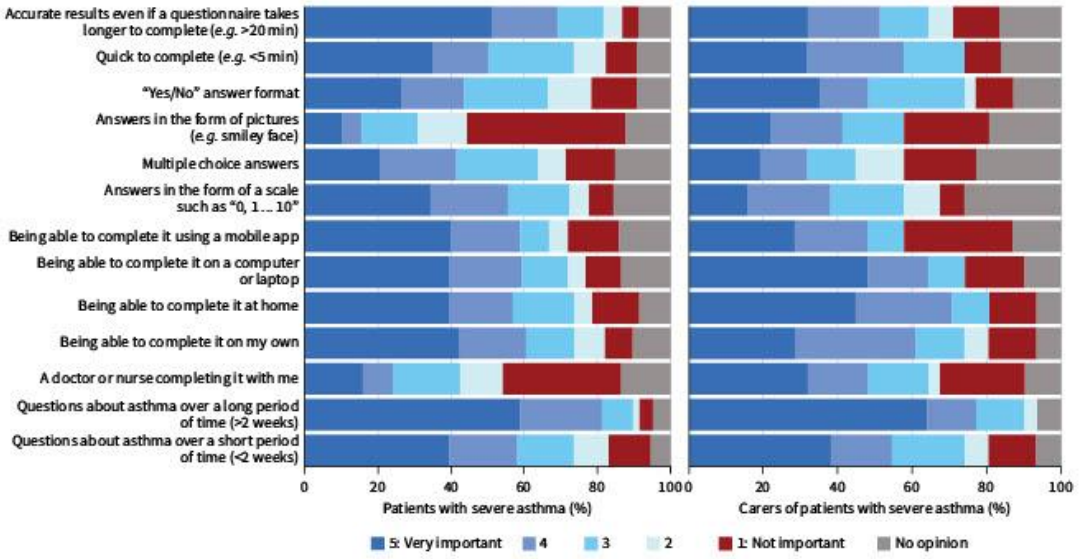

FIGURE 2 Patients' and carers' views about characteristics of questionnaires for assessment of severe asthma according to the pan-European survey.

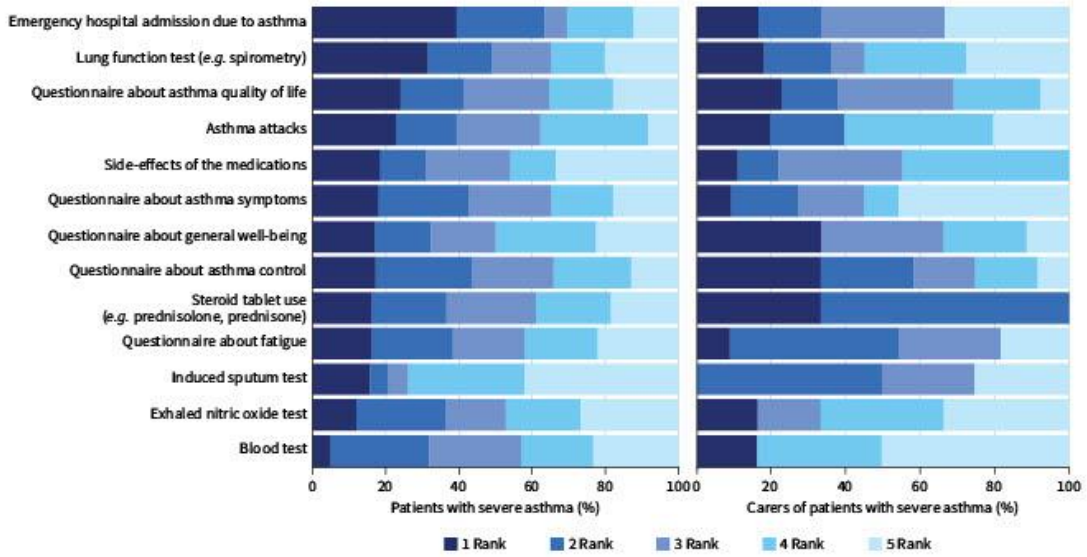

FIGURE 3 Overall views of patients and carers about outcome measures for assessment of severe asthma according to the pan-European survey. Respondents were asked to select five outcome measures and rank their importance from 1=most important to 5=least important, for use in future severe asthma trials and clinical practice.

asthma" (64% and 29%), "lung function" (49% and 36%), "QoL questionnaires" (42% and 39%), "exacerbations" (40% and 40%) and "OCS use" (37% and 100%) (figure 3).

Stage 3: Multi-stakeholder consensus meetings

Adult COM set

A total of 35 participants comprised the multi-stakeholder panel for the adult COM set consensus meeting: 19 (54%) clinicians, nine (25%) patients and patient advocates, four (11%) health regulators, and three (9%) pharmaceutical representatives. The main discussions about the priority outcome measures are summarised in the following subsections and results of the final COM set reported at the end of the section.

Asthma-specific QoL questionnaires

Four instruments were considered: Asthma Quality of Life Questionnaire (AQLQ) [43–45], Asthma Quality of Life Questionnaire-Standardised (AQLQ-S) [45, 46], Mini Asthma Quality of Life Questionnaire (Mini-AQLQ) [45, 47] and Severe Asthma Questionnaire (SAQ) [48–50]. The SAQ had a "moderate" modified GRADE rating for development, whereas other QoL instruments were rated lower [28]. Responsiveness to change was rated "low" to "very low" for all questionnaires; MCID/MID is only reported for the AQLQ and SAQ [50], with the AQLQ MCID being quoted for the AQLQ-S and Mini-AQLQ. Patients highlighted that the Mini-AQLQ might not accurately represent the full AQLQ. The SAQ was highly endorsed as the only questionnaire developed with input from patients with severe asthma and, unlike others, includes items about fatigue and OCS side-effects. Given the novelty of the SAQ, it was suggested that the AQLQ or AQLQ-S should be considered for inclusion in the COM set to allow comparisons with results from previous studies.

Asthma control outcome measures

The Asthma Control Test (ACT) [51–53], Asthma Control Questionnaire (ACQ)-6 (symptoms and rescue medication use) [54–56] and ACQ-5 (symptoms only) [54–56] were discussed at length. None were developed with input from patients with severe asthma and were rated "very low" in terms of development. Responsiveness to change was rated "low" and "very low", but MCID/MID data are available for all instruments. The response format of the ACQ was preferred compared with the ACT by patients, while the ACQ-6 contains an item about rescue medication use which is lacking in the ACQ-5. However, the ACQ-6

does not differentiate between the different rescue medications and their dosing; therefore, it was suggested to report it as the ACQ-5 to describe symptoms and rescue medication use separately.

Composite outcome measure

The Asthma Control and Communication Instrument (ACCI) [57] was rated "low" and "very low" for the developmental and validation process with no data about responsiveness and MCID/MID. Clinicians highlighted that it is rarely used in practice and clinical trials due to the complex scoring system.

Clinical outcome measures

Clinicians noted that FEV_1 change exceeds the MID in some studies with biologics, and it is associated with mortality and future risk of exacerbations [12–14]. Reporting of FEV_1 as z-scores using the Global Lung Function Initiative (GLI) predictive equations [58] was agreed by the panel.

Healthcare resource use

The ATS/ERS definition [25] of severe exacerbation defined as events requiring systemic corticosteroids for ⩾3 days and/or a hospitalisation/emergency room visit for asthma requiring systemic corticosteroids was selected, with exacerbations effectively demonstrating the effectiveness of biologics for different asthma endotypes. However, the more recent ERS/EAACI statement [59] suggests the definition should be based on ⩾5 days of OCS. Annual severe exacerbation frequency should be reported. Use of maintenance OCS (mOCS) defined as daily or alternate day use was considered important for inclusion by all stakeholder groups. Median (25th, 75th centiles) dose and proportion on mOCS should be reported.

TABLE 1 Demographic information about survey respondents in the voting process to agree on the adult COMSA (Core Outcome Measures set for paediatric and adult Severe Asthma)

	Clinicians and researchers			Patient representatives			Pharmaceutical representatives			Health regulators		
	Round 1 (n=30)	Round 2 (n=31)	Round 3 (n=26)	Round 1 (n=11)	Round 2 (n=11)	Round 3 (n=14)	Round 1 (n=3)	Round 2 (n=1)	Round 3 (n=4)	Round 1 (n=5)	Round 2 (n=4)	Round 3 (n=5)
Country												
Belgium	2 (7)	2 (7)	1 (4)									
Denmark	1 (3)	2 (7)										
France	2 (7)		1 (4)									
Germany	2 (7)	2 (7)	1 (4)				1 (33)		1 (25)	4 (80)	3 (75)	4 (80)
Ireland				2 (18)	1 (9)	2 (14)						
Italy	2 (7)	1 (3)		2 (18)	1 (9)	2 (14)						
Netherlands	2 (7)	3 (10)	5 (19)	1 (9)	2 (18)	2 (14)						
Poland	3 (10)	1 (3)	2 (8)									
Portugal				1 (9)								
Spain	1 (3)	1 (3)			1 (9)	1 (7)						
Sweden	3 (10)	6 (19)	4 (15)	2 (18)	2 (18)	2 (14)	1 (33)	1 (100)	1 (25)			
Switzerland									1 (25)			
UK	12 (40)	13 (42)	12 (46)	3 (27)	3 (27)	4 (29)				1 (20)	1 (25)	1 (20)
USA					1 (9)	1 (7)	1 (33)		1 (25)			
Gender												
Male	22 (73)	19 (61)	17 (65)	2 (18)	2 (18)	3 (21)	3 (100)	1 (100)	4 (100)	1 (20)	1 (25)	1 (20)
Female	8 (27)	12 (39)	9 (35)	9 (82)	9 (82)	11 (79)				4 (80)	3 (75)	4 (80)
Age group (years)												
18–25	1 (3)	1 (3)	1 (4)	2 (18)	2 (18)	2 (14)						
26–36	2 (7)	3 (10)	2 (8)	2 (18)	2 (18)	2 (14)						
37–47	6 (20)	8 (26)	9 (35)	2 (18)	3 (27)	4 (29)	1 (33)	1 (100)	3 (75)			
48–58	13 (43)	12 (39)	10 (39)		2 (18)	2 (14)	2 (67)		1 (25)	4 (80)	3 (75)	4 (80)
59–69	8 (27)	7 (23)	3 (12)	4 (36)	1 (9)	2 (14)				1 (20)	1 (25)	1 (20)
70–80			1 (4)	1 (9)	1 (9)	2 (14)						
Online meeting												
Yes	16 (53)	16 (52)	12 (46)	8 (73)	8 (73)	10 (71)	2 (67)	1 (100)	2 (50.0)	4 (80)	3 (75)	4 (80)
No	14 (47)	15 (48)	14 (54)	3 (27)	3 (27)	4 (29)	1 (33)		2 (50.0)	1 (20)	1 (25)	1 (20)

Data are presented as n (%); percentages are rounded to zero decimal places so totals may not add up to 100%.

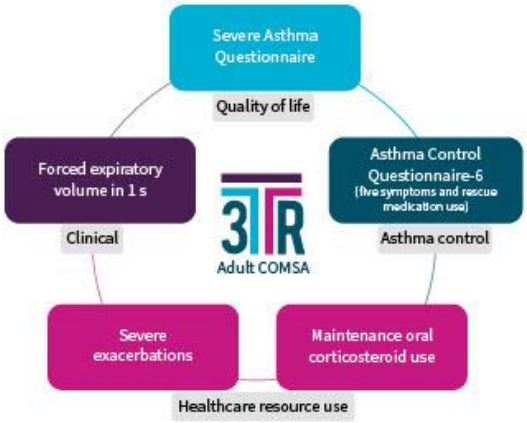

FIGURE 4 The adult Core Outcome Measures set for severe asthma clinical trials. Forced expiratory volume in 1 s should be reported as z-scores using the Global Lung Function Initiative predictive equations [58], annual severe exacerbations as per the European Respiratory Society/American Thoracic Society definition [25] and maintenance oral corticosteroid (mOCS) use defined as daily or alternate day use (median (25th, 75th centiles) dose and proportion on mOCS should be reported). The Asthma Control Questionnaire-6 should be reported as the Asthma Control Questionnaire-5 to describe symptoms and rescue medication use separately. 3TR: Taxonomy, Treatment, Targets and Remission Consortium; COMSA: Core Outcome Measures set for paediatric and adult Severe Asthma.

Ratified COM set for adult severe asthma

The number of participants who voted in each round is listed in table 1. After the third round, five outcome measures reached the 70% consensus threshold and formed the final COM set for adults with severe asthma: SAQ, ACQ-6 (symptoms and rescue medication use reported separately), FEV_1, severe exacerbations and mOCS use (figure 4, supplementary figures S7–S9 and supplementary tables S7–S9). Characteristics and availability of selected outcome measures in the adult COMSA are reported in table 2. No clear consensus was achieved on whether the AQLQ or AQLQ-S should be used in the extended COM set (COM-E). However, a suggestion was made to additionally include the AQLQ in the short term as it includes activities tailored to the patient and would enable retrospective comparisons.

Paediatric COM set

A total of 28 participants comprised the multi-stakeholder panel for the paediatric COM consensus meeting: 13 (46%) clinicians, 12 (43%) patients and patient advocates, and three (11%) health regulators. The main discussions are summarised in the following subsections and results of the final COM set reported at the end of the section.

Asthma-specific QoL questionnaires

The Paediatric Asthma Quality of Life Questionnaire (PAQLQ) [60–63], Paediatric Asthma Quality of Life Questionnaire-Standardised (PAQLQ-S) [60, 62, 63] and Mini-Paediatric Asthma Quality of Life Questionnaire (Mini-PAQLQ) [62, 63] were reviewed. None appear to have been developed with input from patients with severe asthma. Panellists highlighted that when activities are specified (PAQLQ-S) it is easier to compare between patients, but this could be less relevant for individual patients. Responsiveness to change was rated as "low" to "very low". The MCID for the PAQLQ is available and is used for other questionnaires. Some important concepts for severe asthma are not covered in the asthma-specific QoL questionnaires, *e.g.* "missed school days" and fatigue.

Asthma control outcome measures

The ACT (≥12 years) [51, 53], Childhood Asthma Control Test (C-ACT) (4–11 years) [64, 65], ACQ-7 (symptoms, rescue medication use and FEV_1) [54, 56, 66, 67], ACQ-6 (symptoms and rescue medication use) [54, 56, 66] and ACQ-5 (symptoms only) (≥6 years) [54, 56, 66] were discussed. An assessment of control over 4 weeks was suggested to be advantageous. Some clinicians proposed using the ACQ-6 to

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TABLE 2 Characteristics of the questionnaires selected for the adult and paediatric COMSA (Core Outcome Measures set for paediatric and adult Severe Asthma)

Scale (year)	Modes of administration	Target population	Time to complete	Patient/ carer report	Recall period	Number of questions, response format(s)	Scoring method	Original language, translations[#]	Licence and costs
Questionnaires selected for the adult COMSA									
SAQ [48] (2018)	Self-complete; paper form	16–78 years	3–6 min	Patient	2 weeks	SAQ: 16 questions: 7-point Likert scale (1=very, very difficult, 7=no problem); SAQ-global: 100-point QoL scale (0=no QoL, 100=perfect QoL)	SAQ: average of responses (range 1–7); SAQ-global (range 0–100)	English (UK): two validated translations; several unpublished translations	Copyrighted by University of Plymouth and University Hospitals Plymouth NHS Trust; free for non-commercial, clinical practice and research; fees may apply for funded research, healthcare organisations, commercial use
ACQ-6 [55][¶] symptoms and rescue medication (2001)	Self-complete; paper form; interactive web; electronic devices	⩾6 years	Not reported	Patient	1 week	Six questions: 7-point Likert scale (0=no impairment, 6=maximum impairment)	Average of responses: range 0–6	English (UK): 111 translations	Copyrighted by questionnaire developer, QOL Technologies Ltd; free for non-commercial, clinical practice and research; otherwise, there is a one-time fee; electronic version requires a user fee
Questionnaires selected for the paediatric COMSA									
PAQLQ [60] (1996)	Self-complete; paper form; interviewer-administered version (⩽11 years)	7–17 years	10–15 min at initial visit; 5–10 min at follow-ups	Patient	1 week	23 questions: 7-point Likert scale (1=severe impairment, 7=no impairment)	Three subscales: average of responses; range 1–7	English (North America): 62 translations	Copyrighted by questionnaire developer, QOL Technologies Ltd; free for use in non-commercial, clinical practice and research; otherwise, there is a one-time fee

Continued

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TABLE 2 Continued

Scale (year)	Modes of administration	Target population	Time to complete	Patient/ carer report	Recall period	Number of questions, response format(s)	Scoring method	Original language, translations[#]	Licence and costs
C-ACT [65] (2007)	Self-complete; paper form; web-based	Children and carers of children aged 4–11 years	Not reported, but web-based version takes 5 min to complete	Patient and carer	4 weeks	For children (four questions): 4-point Likert scale (0="very bad", 3="very good"; including pictures of a child's face with matching expressions); for carers (three questions): 6-point Likert scale (0="everyday", 5="not at all")	Sum of the item responses; range 0–27 (⩽19 points= uncontrolled asthma)	English (USA): 27 translations	Copyrighted by GlaxoSmithKline Ltd; free for non-commercial, clinical practice and research; fee may apply for commercial use
ACT [51] (2004)	Self-complete; interviewer-administered; paper form; web-based; telephone	⩾12 years	1–2 min	Patient	4 weeks	Five questions: 5-point scale (questions about symptoms and activities: 1=all the time, 5=not at all); patient self-rating of control: (1=not controlled at all, 5=completely controlled)	Sum of the item responses; range 5–25 (⩽19 points= uncontrolled asthma)	English (USA): 179 translations	Copyrighted by Quality Metric Inc.; permission required for use

SAQ: Severe Asthma Questionnaire; QoL: quality of life; ACQ: Asthma Control Questionnaire; PAQLQ: Paediatric Asthma Quality of Life Questionnaire; C-ACT: Childhood Asthma Control Questionnaire; ACT: Asthma Control Test. [#]: the number of translations is an estimate sourced from sites and manuals of the instruments available in English; [¶]: the ACQ-6 should be reported as the ACQ-5 to describe symptoms and rescue medication use separately.

harmonise the paediatric COM set with the adult COM set and facilitate transition between services. Patient advocates expressed a particular preference for the ACT and C-ACT as they both include a global question about self-rating of control.

Composite outcome measure

The Composite Asthma Severity Index (CASI) [68, 69] was deprioritised as it does not include items relating to QoL and activity limitations, and was not developed with patient input.

Clinical outcome measures

Most children aged ⩾5 years can perform spirometry reliably [70]. FEV_1 may not always reflect the current degree of asthma control [71]; however, clinicians suggested that low FEV_1 predicts future risk of exacerbations, which is also supported by the literature [72]. Reporting of FEV_1 as z-scores using the GLI predictive equations [58] was agreed by the panel. Most participants felt that F_{ENO} was a useful biomarker in understanding and managing asthma [73], although consensus was not reached for it to be one of the patient-centred COM.

Healthcare resource use

Exacerbation was ranked within the top five most important outcome measures by patients in the pan-European survey and shown to have good responsiveness to change in different biologics. The panel agreed to use annual frequency of severe exacerbations defined by the ATS/ERS definition [25].

mOCS use as per the adult COM was selected. Some clinicians thought that mOCS use was not important for children as it is used very infrequently; however, others noted that reduction in OCS use is a major criterion to assess whether a biologic has been effective. Additionally, carers in the pan-European survey indicated that OCS use is one of the most important aspects, especially due to the associated side-effects. Being treated with mOCS was selected as OCS bursts should be captured by severe exacerbations.

Ratified COM set for paediatric severe asthma

After the second round of voting, five outcome measures for paediatric severe asthma reached the 70% consensus threshold: FEV_1, severe exacerbations, PAQLQ, mOCS use and ACT/C-ACT (table 3, figure 5, supplementary figures S10 and S11, and supplementary tables S10 and S11). Characteristics and availability of selected paediatric COMSA are reported in table 2.

Discussion

In this multi-step consensus process involving four key stakeholder groups, we developed adult and paediatric COM sets to standardise outcome reporting for severe asthma biological trials. Through multi-stakeholder consensus meetings and multiple rounds of voting, we identified five COM for adult and paediatric clinical trials that are important to patients, clinicians, pharmaceutical representatives and health regulators. Our recommendations were informed by data from a pan-European survey and a narrative literature review, plus the developmental and validation process including applicability for severe asthma, responsiveness to change and availability of MCID from systematic reviews.

The COM sets we present are novel since they focus specifically on severe asthma. The COMSA initiative builds on the coreASTHMA project that aimed to harmonise collection and reporting of outcomes in patients with moderate-to-severe asthma [23]. Both initiatives selected exacerbations, asthma-specific QoL and change in asthma control as core outcomes; however, COMSA aimed to select specific outcome measures to assess QoL and asthma control, and also included FEV_1 and mOCS use. Furthermore, coreASTHMA included asthma-specific emergency department visits and asthma-specific hospital stay or admission. These outcomes were discussed by the COMSA panellists in multi-stakeholder discussions prior to the consensus meeting, and were excluded due to variable admission protocols and differences in healthcare settings.

Using PROM is important to understand the effect of asthma treatment on patients' QoL and experience with biological treatment. Panellists strongly advocated the inclusion of the SAQ in the adult set; although currently validation data are only available for the UK and Portugal populations, further studies are underway to adapt the SAQ to other languages, settings and for children. The advantages of using this outcome measure were that it is the only instrument that is developed for severe asthma patients and scored well for validation and reliability. However, while the AQLQ has a longer history and experience in use, it was not specifically developed for severe asthma and does not assess side-effects of OCS use and the psychological burden for these patients.

TABLE 3 Demographic information about survey respondents in the voting to agree on the paediatric COMSA (Core Outcome Measures set for paediatric and adult Severe Asthma)

	Clinicians and researchers		Patient representatives		Pharmaceutical representatives		Health regulators	
	Round 1 (n=36)	Round 2 (n=34)	Round 1 (n=13)	Round 2 (n=9)	Round 1 (n=1)	Round 2 (n=2)	Round 1 (n=3)	Round 2 (n=3)
Country of residence								
Denmark	1 (3)	1 (3)						
France	2 (6)	1 (3)						
Germany	2 (6)	1 (3)					3 (100)	3 (100)
Ireland			1 (8)	1 (11)				
Italy	2 (6)	2 (6)	2 (15)	1 (11)				
Netherlands	4 (11)	3 (9)	1 (8)					
Poland	2 (6)	1 (3)						
Sweden	4 (11)	4 (12)	5 (39)	3 (33)		1 (50)		
Switzerland	1 (3)	2 (6)						
Turkey	1 (3)	1 (3)						
UK	17 (47)	18 (53)	3 (23)	3 (33)				
USA			1 (8)	1 (11)	1 (100)	1 (50)		
Gender								
Male	19 (53)	19 (56)	2 (15)	1 (11)	1 (100)	2 (100)		
Female	17 (47)	15 (44)	11 (85)	8 (89)			3 (100)	3 (100)
Age group (years)								
12–17			3 (23)	1 (11)				
18–25	1 (3)	1 (3)	2 (15)	2 (22)				
26–36	2 (6)	2 (6)	2 (15)	2 (22)				
37–47	9 (25)	7 (21)	3 (23)	3 (33)		1 (50)		
48–58	14 (39)	15 (44)	1 (8)	1 (11)		1 (50)	3 (100)	3 (100)
59–69	8 (22)	7 (21)	1 (8)					
70–80	2 (6)	2 (6)	1 (8)					
Prefer not to say					1 (100)			
Online meeting								
Yes	21 (58)	21 (62)	8 (62)	6 (67)			3 (100)	2 (67)
No	15 (42)	13 (39)	5 (39)	3 (33)	1 (100)	2 (100)		1 (33)

Data are presented as n (%); percentages are rounded to zero decimal places so totals may not add up to 100%.

Generic outcome measures (*e.g.* generic QoL instruments) were not selected, but we acknowledge they are imperative to facilitate comparisons of burden across diseases and cost-effectiveness analysis of biological therapies [74, 75]. The AQLQ would also be more appropriate for asthma studies enrolling mild, moderate and severe participants.

Identifying an asthma control instrument that would be relevant for severe asthma was noted as a challenge. The Global Initiative for Asthma 2021 report recommends using maintenance and reliever therapy (MART) for adolescents and adults with asthma at all treatment steps, and prefers the ACQ-5 as the ACQ-6 rescue question is not valid for MART [76]. However, the ACQ-6 was rated as a more relevant outcome measure for the COM set, but it should be reported as the ACQ-5 (asthma symptoms) and rescue medication use separately. Lastly, during the consensus process it was suggested that trials should record comorbidities as many patients, especially children and adolescents, have other allergic conditions and several biologics can impact on more than one disease. However, the focus of this work is severe asthma and it was suggested that separate COM should be considered for other comorbidities.

Strengths and limitations

Our study has several strengths. The COMSA was developed through a methodologically robust and multinational consensus process according to the modified guidance from the COMET initiative. It incorporated perspectives from four stakeholder groups including patients with severe asthma from across Europe. Translators were available for patients to prevent any selection bias and incorporate wider patient perspectives during meetings and online voting. Additionally, qualitative analysis of comments from the multilingual pan-European survey allowed further representation of views of patients and carers.

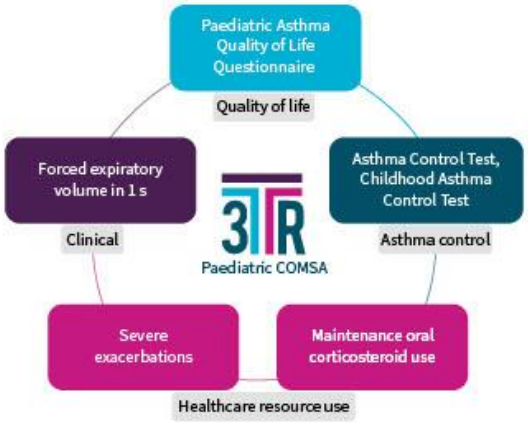

FIGURE 5 The paediatric Core Outcome Measures set for severe asthma clinical trials. Forced expiratory volume in 1 s should be reported as z-scores using the Global Lung Function Initiative predictive equations [58], annual severe exacerbations as per the European Respiratory Society/American Thoracic Society definition [25] and maintenance oral corticosteroid (mOCS) use defined as daily or alternate day use (median (25th, 75th centiles) dose and proportion on mOCS should be reported). The Childhood Asthma Control Test should be used for children 4–11 years old and the Asthma Control Test should be used for children 12–18 years old. 3TR: Taxonomy, Treatment, Targets and Remission Consortium; COMSA: Core Outcome Measures for paediatric and adult Severe Asthma.

Throughout the project, researchers collaborated with ELF and EFA representatives who have extensive experience of working with patients to ensure comprehensibility of the process. Furthermore, we used a systematic and transparent approach in assessing the development and measurement properties of priority outcome measures by applying COSMIN guidelines and synthesised the evidence using the modified GRADE approach [30–32]. Lastly, having online consensus meetings and voting allowed an interactive exchange of views from a wider range of representatives from across Europe.

We acknowledge some limitations. We aimed to develop patient-centred COM sets; however, some COM were not highly favoured from the patient perspective. Furthermore, the systematic review did not identify any validation data for the priority clinical and healthcare use measures for severe asthma, so decisions were based on expert consensus. Although a considerable number of expert clinicians, patients with severe asthma, patient representatives, pharmaceutical representatives and health regulators were involved from across Europe, it would have been useful to have included more, especially from the latter two groups. It would also have been helpful to have additional non-UK clinicians, although we had good involvement of healthcare professionals. We chose to include a relatively low number of patient representatives to ensure that we could provide them considerable support and training to allow them to provide meaningful input into the development process. This limitation was mitigated by the pan-European patient survey which widened the input of patient views. Lastly, it is important to highlight that COMSA is a minimum set only and other outcome measures could also be included by study investigators according to their research needs.

Research agenda

The development of a QoL outcome measure specifically for children and adolescents with severe asthma was identified as a major unmet need. Currently, paediatric QoL PROM do not assess all possible impairments such as anxiety and activity limitations specific to severe asthma. As highlighted by the PWG and pan-European survey, most of the questionnaires are not accessible online or *via* a mobile app, thus further development and validation is needed. Furthermore, there is an unmet need for long-term outcomes, and also importantly, disease-modifying outcome measures in severe asthma including disease remission.

Panellists also noted that side-effects of OCS and biologics, and adherence to therapy, should be considered as important outcome measures. Due to the lack of validated and reliable methods of collecting these data

as well as data for the clinical and healthcare outcome measures for severe asthma, this was considered as a research gap. Therefore, the COMSA should be updated once new data are available. Researchers should also develop a more robust means of measuring reliever use that takes into account the different relivers such as salbutamol, terbutaline and the MART approach. Lastly, there is also a need for data specifically from paediatric studies with biologics to assess responsiveness to change of outcome measures.

Conclusions

In conclusion, we have developed evidence-based and patient-centred COM sets for paediatric and adult severe asthma biological therapy trials. The COMSA should be recommended to increase consistency in reporting of outcome measures, and to improve comparability of studies and certainty of evidence to guide policy making and clinical practice. These COM sets will inform future work for the development of definitions of response and non-response to biological therapies for severe asthma. Regular review and updates are necessary to ensure that the COM sets reflect current clinical practice. There is a need to develop an approach for monitoring implementation of these COM sets and global uptake of the agreed COM in research and practice.

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Publication 2 supplement

Development of Core Outcome Measures sets for paediatric and adult Severe Asthma (COMSA).

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Table S1. Core Outcome Set-STandards for Reporting.

Section/Topic	#	Checklist item	Reported
TITLE/ABSTRACT			
Title	1a	Identify in the title that the paper reports the development of a COM set	✓
Abstract	1b	Provide a structured summary	✓
INTRODUCTION			
Background and Objectives	2a	Describe the background and explain the rationale for developing the COM set.	✓
	2b	Describe the specific objectives with reference to developing a COM set.	✓
Scope	3a	Describe the health condition(s) and population(s) covered by the COM set.	✓
	3b	Describe the intervention(s) covered by the COM set.	✓
	3c	Describe the setting(s) in which the COM set is to be applied.	✓
METHODS			
Protocol/Registry Entry	4	Indicate where the COM set development protocol can be accessed, if available, and/or the study registration details.	✓
Participants	5	Describe the rationale for stakeholder groups involved in the COM set development process, eligibility criteria for participants from each group, and a description of how the individuals involved were identified.	✓
Information Sources	6a	Describe the information sources used to identify an initial list of outcomes.	✓
	6b	Describe how outcomes were dropped/combined, with reasons (if applicable).	✓
Consensus Process	7	Describe how the consensus process was undertaken.	✓
Outcome Scoring	8	Describe how outcomes were scored and how scores were summarised.	✓
Consensus Definition	9a	Describe the consensus definition.	✓
	9b	Describe the procedure for determining how outcomes were included or excluded from consideration during the consensus process.	✓
Ethics and Consent	10	Provide a statement regarding the ethics and consent issues for the study.	✓
RESULTS			
Protocol Deviations	11	Describe any changes from the protocol (if applicable), with reasons, and describe what impact these changes have on the results.	NA
Participants	12	Present data on the number and relevant characteristics of the people involved at all stages of COM set development.	Table 1,2
Outcomes	13a	List all outcomes considered at the start of the consensus process.	Ref 28
	13b	Describe any new outcomes introduced and any outcomes dropped, with reasons, during the consensus process.	Ref 28
COM set	14	List the outcomes in the final COM set	Figure 4, 5
DISCUSSION			
Limitations	15	Discuss any limitations in the COM set development process.	✓
Conclusions	16	Provide an interpretation of the final COM set in the context of other evidence, and implications for future research.	✓
OTHER INFORMATION			
Funding	17	Describe sources of funding/role of funders.	✓
Conflicts of Interest	18	Describe any conflicts of interest within the study team and how these were managed.	✓

Adapted from Kirkham et al[1]. COM: Core Outcome Measures set. NA, not applicable. Tick indicates 'yes'.

I. Narrative review to capture patients' perceptions and opinions about selected outcome measures for severe asthma.

1. Introduction

The aim of this narrative review was to synthesise evidence about patient perceptions and opinions about selected outcome measures for severe asthma, as part of the IMI 3TR project. The findings from this review will help to inform discussions in a multi-stakeholder consensus workshop to agree on a core outcome measures (COM) set for use in severe asthma research.

This review was conducted by the European Lung Foundation (ELF) team in collaboration with the University of Southampton Research team.

2. Methods

2.1. Data sources and search strategy

Three bibliographic databases were searched (Embase (OVID); CINAHL (EBSCOhost, Cumulative Index to Nursing and Allied Health Literature); PsycINFO (EBSCOhost)) from the year 2000 to 11th November 2020. The search strategy was developed on EMBASE (OVID) and subsequently adapted for other databases. Additional references were identified through discussion with experts in the field.

2.2. Study selection

- Patient characteristics: adults and children (aged ≥6 years) with a diagnosis of severe asthma.
- Phenomenon of interest: patient experiences of outcome measures used to monitor severe asthma. The outcomes of interest were previously selected during a modified Delphi exercise.
- Designs: qualitative studies including focus groups, interviews, and quantitative studies with a qualitative element including surveys and randomised controlled studies.
- Evaluation: views, attitudes, beliefs, experiences, and preferences.
- Research type: qualitative and mixed-methods.
- Language: English

The following were excluded: systematic reviews and meta-analyses, narrative reviews, discussion papers, editorials, commentaries, case studies, animal studies, conference abstracts, studies not available in full form, unpublished material, non-asthma studies (e.g. viral bronchiolitis or viral associated wheeze), studies conducted with exclusively mild or moderate asthma populations.

2.3. Data extraction, synthesis, and analysis

Data extraction was done in duplicate (CC, CW). The following data were extracted: country, patient characteristics, number of participants, study design, outcome(s) of interest, asthma definition, severity, and treatment, and whether it was possible to separate views of severe asthma patients if the study included participants with a range of severities (mild to severe). The main findings are described narratively, and key themes are summarised.

3. Results

3.1 Search results

The systematic literature search produced 127 papers. 7 papers met the inclusion criteria and were included in

the review **(Figure S1).**

3.2 Characteristics of included studies

No qualitative studies specifically explore patients' experiences of outcome measures which are used to assess and monitor response to treatment for severe asthma. Most of the included studies aimed to understand the severe asthma patients' experience of disease management and treatment, where this included patients' views on the outcome measures of interest. One study was a randomised controlled trial with a qualitative element to assess peak expiratory flow (PEF) meter use in childhood including the perceived usefulness and burden.[2] Six studies included adult patients[3-8]; one study focused on children aged between 6 and 19 years.[2] Studies included severe asthma populations in Australia, UK and US.

Patient perspectives were available on the following outcome measures of interest and are presented below:

- Peak expiratory flow monitoring
- Hospitalisation
- Exacerbations
- Adverse events
- Reducing oral corticosteroid use (steroid sparing)

Additionally, treatment burden was identified as an important factor relevant to several outcome measures and patient perspectives on this topic are therefore presented below.

3.3 Patient perspectives about selected outcome measures

3.3.1. Peak expiratory flow monitoring

Some patients feel confident using peak flow to monitor symptoms and respond accordingly. However, most studies reported that patients use peak flow monitoring only at times of worsening asthma control, if at all, and to help them decide when to seek emergency help.[2,3,5] The unpredictability of severe asthma contributes to patients' difficulty in monitoring and managing symptoms, including when peak flow readings do not align with other objective tests:

> "When I saw [Consultant] he said your eosinophils are raised. I said oh that's strange because my peak flow hasn'tmoved. And that did really throw me a bit, I must admit, in that I'd always relied on the peak flow to be the marker of when to start taking steroids."[3]

Children and adolescents feel that daily peak flow monitoring is too burdensome, and that the burden outweighs the potential benefit: "fun at first, then became a chore". Peak flow was considered more useful as a monitoring tool during symptomatic periods. Children with more frequent symptoms are more likely to continue peak flow use, suggesting that patients with severe asthma may find it more useful than those with moderate asthma. Parents consider peak flow to provide useful information and reassurance.[2]

Several studies reported that patients delay seeking emergency help, even when their peak flow reading is below the agreed cut-off to call an ambulance:

> "I usually call the ambulance around about the time where if I'm like, less than 100. I'm supposed to call the ambulance at 250."[5]

> "I don't always get to follow it [Action Plan] as I should obviously because I'm a single mum. There are times, it's like I'm blowing peak flows of like 120 and they [Healthcare professionals] say that if I get to 150 that's when I should ring 999, but I just sit up in a locked room. With my ioniser and my steroids and my Ventolin just trying to not take deep breaths".[3]

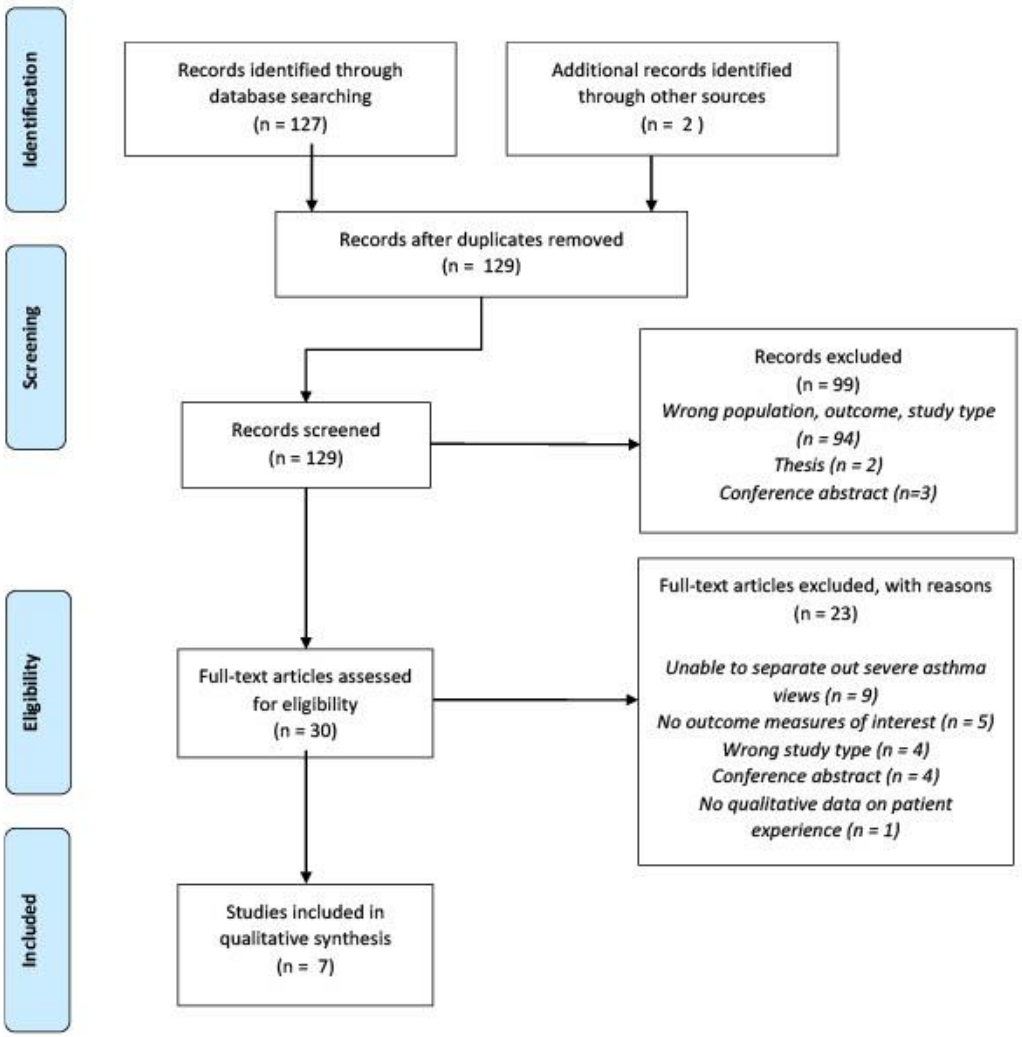


Figure S1. PRISMA diagram showing study selection.

3.3.2. Hospitalisation

Patients want to avoid hospitalisation for a range of reasons including the emotional impact, the disruption to their life, and a firm desire to self-manage.[3,5,6,8] Some patients have a strong dislike of the environment, even if they have previously been satisfied with their hospital care: "You don't have to keep going over the same information... it's just streamlined...they don't muck around."[5] Hospitalisation may also cause anxiety about the severity of the individual's asthma and potential decline in future health:

> "I don't like coming to hospitals and I don't like coming to doctors surgeries, particularly don't like coming here [hospital], because I kind of look around and sort of see the future me. And I don't want to be like that. I'd do anything not to be like that, and that does bring me down quite a lot."[3]

Hospitalisation is considered disruptive to the individual's life and many prioritise their family or work commitments over their own health. Patients also report social pressure and the desire to 'keep up' with others as a reason for delaying emergency care:

> "Being in a state where I probably should've been in hospital because my lung function was that bad ... having

to get it done [at work] because the guy standing next to you is perfectly healthy … and you've got to keep up with him."[6]

"When I went to the GP last week, my peak flow was 150, and on my card it says I have to go straight to [hospital], and I said to the nurse I can't, I haven't got time to."[3]

The long-term impact of hospitalisation can be far-reaching. Frequent hospital admissions may impact a person's ability to work: "I lost my job, I was medically discharged because I was in and out of hospital."[8] There are also residual effects during the time after leaving hospital, when an individual is expected to resume their usual caring or other commitments while still unwell:

"Of course when you come out of hospital, because they've done you a favour it's like, '"I'm out of hospital, I'll have the boys back."'[8]

Several studies reported a strong desire to self-manage asthma at home and to avoid hospitalisation:

"The way I look at it, I've got the nebuliser at home, I've got the medication given me here anyway, I've got the peak flow. I can do everything in the comfort of my own home. The only thing that I don't have at home is people coming round every three hours taking blood out of me, which I don't like needles."[3]

3.3.3. Exacerbations

Clark *et al* collected patient perspectives on exacerbations as a treatment outcome.[4] Reducing the number and severity of asthma attacks is an important treatment priority for severe asthma patients, who rated it as the second most important outcome after quality of life. The majority of patients included it within their top five outcomes of importance.

Clark *et al* found no significant differences in outcome ratings for participants currently prescribed a biological therapy to those that were not; the duration of biological therapy prescription; and those who were on maintenance OCS (daily) compared to those who were not.[4]

3.3.4. Adverse events

Patients have concerns about treatment side effects (adverse events) in the short and long-term. Clark *et al* asked patients to consider hypothetical scenarios and make a choice between severe asthma medications (3 injectable biological therapies; 1 antibiotic tablet). Side effect profile is the primary factor which patients consider important, and azithromycin tablet was the preferred treatment based on side effect profile. When treatment efficacy, logistics and side effect profile were considered in combination, benralizumab was the preferred treatment for 68% of patients, with azithromycin selected by 26%.[4]

Patients' worries about side effects are almost exclusively linked to oral corticosteroids (OCS). Concerns relate to bone, skin, liver and dental health, gastric problems, diabetes, weight gain, depression and other mood changes, irritability, sleep disturbance, hunger and disturbed eating patterns, changes in facial appearance, pain, and anxiety about medication and about future disease course.[3,5-8] While some quality of life questionnaires address some of these domains, they may monitor them exclusively in relation to asthma symptoms or asthma control, thus overlooking the complications resulting from OCS use – for example, questions on sleep disturbance caused by asthma may overlook patients whose sleep is disturbed by OCS.[8]

For many patients, their concerns are based on OCS side effects they have already experienced, as well as knowledge of the drug's side effect profile and reports from peers.[3,6-8] While participants in Gamble *at* al's study reported physical side effects such as weight gain and osteoporosis, the predominant issue of more concern to patients was psychological disturbances (anxiety, irritability, depression). Patients talk about a loss of identity as a result of OCS treatment, encompassing a range of physical and psycho-social factors – changes to their personality and appearance, inability to fulfil their normal role in the family unit, being perceived as different by family and

friends.[7] The impact of OCS treatment affects patients' lives and the lives of their family on a daily basis.[7]

Some patients had experience of very severe side effects including Addison's disease and avascular necrosis.[6] One patient reported steroid-induced psychosis.[7] Patients also have more general concerns about using high dose OCS for long periods, and potential future side effects such as osteoporosis and cataracts.

> "Well, I don't like steroids. Obviously, they work extremely well to reduce the inflammation but with side effects. Ido bruise easily, my skin is extremely thin and the potential for perhaps developing diabetes, which one of my friends did, and also glaucoma as well or cataracts rather, doesn't fill me full of joy and excitement really!"[3]

> "I'm getting cataracts, and I'm getting necrosis in the hips ... my skin's thinning down, my dental health's gone down just completely and all my beautiful teeth started falling out. Eh, all these side effects um, started accumulating. And it's all because of the steroids...then of course the most scariest one for me was the fact that the gland that produces your natural corticosteroid after extreme long-term use can, can atrophy and wither away to nothing and then your body can never produce enough natural steroid ever again."[6]

> "I didn't realise until I started taking them just the effect they could have on you mentally. I would say I suffer from depression. The psychiatrist reckoned that I have a steroid induced psychosis. I battle with myself every time I feel the asthma getting worse. I probably think I should have them upped at the minute...but I keep thinking to myself maybe it'll go away. It's like a bomb waiting to explode."[7]

> ''I cannot manage without the maintenance dose. I can't let [husband] touch me because my skin feels as if it's all bruising''.[8]

Hyland *et al* note that, regardless of whether patients' attribution of certain side effects to OCS is a true reflection of the medication's effects, the belief that OCS causes these effects is real and can impact on treatment adherence and asthma control.[8]

One patient reported an irregular heartbeat from bronchodilator use, and had a pacemaker as a result.[6] Patients in several studies perceived asthma medications, other than OCS, as having no or trivial side effects, although it should be noted that they were conducted before many of the current biological treatments for severe asthma were available.[7,8]

3.3.5. Reducing oral corticosteroid use (steroid sparing)

Reducing OCS use is an important outcome to patients. Clark *et al* found it to be the fifth most important treatment priority, both for patients on daily OCS and for those taking OCS as needed.[4]

Some participants in Donald *et al's*[5] and Gamble *et al's* studies described intentional non-adherence, delayed initiation of OCS treatment, or aiming to reduce the amount of OCS taken, against medical advice: "They said I could take it for 3 weeks, but after 3 days I said yes, well, I'm okay, going to avoid it".[7] Other studies found non-adherence to be low, with patients reporting that they weigh up the risks and benefits of OCS treatment, with most concluding that treatment is necessary in order to stay well.[3,8] For patients, there is a 'constant internal battle' to comply:

> "But without them [OCS] I wouldn't be here... So it's weighing those...If I didn't have them I might not be here might I? So that's how I look at it and I could be dead if I didn't take them".[3]

Nevertheless, the studies support the overall theme across the literature of reducing OCS use as an important treatment priority for severe asthma patients.[3-5,8] In two studies patients indicated that OCS had a greater impact on their lives than asthma symptoms.[7,8] Several patients said that they would trade up to 15 years of life in order to stop OCS treatment with asthma symptoms remaining constant.[8] One patient described reducing steroid dependence as their treatment goal when starting a monoclonal antibody treatment:

> "The only thing that...which is the thing I'm waiting for now, is to be put onto this course of injections rather than taking this...it won't be rather than taking the steroids but with a view to reducing the steroid dose. That will be my ultimate aim."[3]

3.3.6. Treatment burden

Factors related to the burden of treatment, over and above side effect burden, were reported in four of the seven studies.[4-7] While treatment burden and related factors are not outcome measures in themselves, it is important to take into account patient perspectives of this topic, particularly given the cross-cutting relevance to several of the outcome measures.

Patients reported concerns around the inconvenience of attending hospital for regular injectable treatment[4,6], the cost of treatment[4-6] and the time needed to take daily treatment.[6,7] As with other aspects of asthma self-management, patients may choose to prioritise family and work commitments over their own health.[7]

> "Well you have to go to your GP 'cos there's a risk of anaphylaxis. Um, so you've got to be there, And I've got to have a bloody EpiPen in my bag every time I go there in case I have a reaction. Yeah, it's a bit of a cumbersome kind of system. Um, my GP, it's a bit of a drive for me and I've gotta put away, basically put 1 day aside virtually every fortnight to go and get this all done".[6]

> "And I've already worked out that the day I stop working and can't financially support myself I should be as good as dead because I can't afford to maintain this illness without working and having a good salary".[6]

> "The nebuliser takes up quite a lot of time in the mornings when you are getting ready with the kids and things like that for school."[7]

Logistics and burden of treatment were ranked as the third most important factor for patients when choosing between two or more medications and patients weigh up a range of factors when making treatment decisions: "Whilst 'asthma treatment efficacy' was considered the most important factor for decision-making, approximately one-quarter of patients selected a medication that was not consistent with this preference when the hypothetical scenarios were presented collectively. These participants traded off asthma treatment efficacy in favour of how the medication is administered and the side-effect profile, and their preferred medication was a tablet [...] This indicates that for a subgroup of patients, a medication's performance in improving asthma related outcomes alone is not enough information for them to make a fully informed choice regarding their treatment options."[4]

Treatment burden is an important factor for patients and should be considered when evaluating severe asthma treatments. Aspects of treatment burden may include a range of factors, such as the cost to patients of objective testing, the availability of and access to tests across diverse health systems in Europe, and the frequency of testing required to accurately monitor severe asthma control. Some patients place more importance on treatment burden than others.

4. Discussion

This narrative review provides an important synthesis of previous research into the views of patients with severe asthma about selected outcome measures. The findings reported here will be discussed in a multi-stakeholder consensus workshop to agree on a core outcome measures (COM) set for use in severe asthma research.

There are some limitations to this review. Firstly, the search was restricted to articles published in English. However, experts in the field were consulted so it is unlikely that any relevant articles were missed. Patients treated within European health systems, apart from the UK, were not represented in the included studies and this may limit the generalisability of these findings. This may be due to a lack of research or to the search being limited to the English language.

Secondly, we searched the databases for articles published only in the last 20 years. This was done so that the literature reflected the modern approach to severe asthma management with biological therapies. Lastly, there is no single definition of severe asthma used across the included studies. Studies were included where the researchers defined participants as having severe asthma, although their criteria were not always reported.

Overall, there is a lack of qualitative data to understand patient experiences and preferences around severe asthma treatment outcomes, particularly in the era of biological treatment. To help address this gap, a survey has been conducted as part of the 3TR project to better understand the views of patients and carers with severe asthma about outcome measures.

Limited research has been done to understand patient perspectives on outcome measures in severe asthma. Qualitative research is needed to highlight patient views on this topic, particularly to understand perspectives on the outcome measures of interest for which no qualitative literature was found during this review.

Avoiding hospitalisation, reducing OCS use and related side effects, and reducing the number and severity of exacerbations are all treatment priorities for patients, and individual patients weigh up a range of factors when making choices about their treatment and care. Moreover, different patients place higher importance on certain outcomes - there is no 'one size fits all' outcome. In order to ensure that patients can make informed treatment choices, clinical research must measure a range of patient-centric outcomes, and patients must have access to information about the benefits, disadvantages and differences between treatment options.

Future research should also develop and validate outcome measures which address the aspects of severe asthma, such as fatigue, long-term OCS use and side effects, and healthcare utilisation which are of high importance to patients, but for which there are currently no outcome measures.

Search strategy for EMBASE (OVID)

1. severe persistent asthma/

2. (severe adj5 asthma*).mp.

3. 1 or 2

4. peak expiratory flow.mp. or peak expiratory flow/ or PEFR.mp. or PFR.mp. or PEF.mp.

5. FEV1.mp. or forced expiratory volume/

6. forced expiratory volume in 1 second.mp.

7. forced expiratory volume in one second.mp.

8. forced vital capacity/ or forced vital capacity.mp.

9. FEV1?FVC.mp.

10. fractional exhaled nitric oxide/

11. FeNO.mp. or nitric oxide/ or eNO.mp. or exhaled NO.mp. or (nitric* adj1 oxide*).mp.

12. eosinophil*.mp. or exp eosinophil/ or exp eosinophil count/

13. (P?ediatric asthma quality of life questionnaire* or Mini-P?ediatric asthma quality of life questionnaire* or mini-PAQLQ or PAQLQ).mp.

14. Pediatric Quality of Life Inventory/ or P?ediatric Quality of Life Inventory.mp. or PedsQL.mp. or PedsQLTM.mp.

15. (Asthma Quality of Life Questionnaire* or AQLQ).mp.

16. (Mini-Asthma Quality of Life Questionnaire* or mini AQLQ-J or mini-AQLQ or miniAQLQ).mp.

17. (Severe Asthma Questionnaire* or SAQ).mp.

18. (Child Health Survey for Asthma-Child Version or CHSA-C).mp.

19. (Asthma Quality of Life Questionnaire Marks or AQLQ-M).mp.

20. (Asthma Short Form or ASF).mp.

21. short form 36/ or Short Form 36 Health Survey.mp. or SF36.mp. or 36 item short form health survey.mp. or short form 36.mp.

22. (PROMIS p?ediatric global health scale or PGH-7).mp.

23. (Kids-CAT or Kids computer-adaptive test*).mp.

24. (Fatigue Severity Scale or FSS).mp.

25. Functional Assessment of Chronic Illness Therapy Fatigue.mp. or exp "functional assessment of chronic illness therapy fatigue scale"/ or FACIT fatigue.mp. or FACIT-F.mp.

26. (Epsworth Sleepiness Scale or ESS).mp.

27. exp "european quality of life 5 dimensions 5 level questionnaire"/ or european quality of life 5 dimensions 5 level questionnaire*.mp. or EQ*-5D-5L.mp. or EQ5D5L.mp. or Euro* Quality of Life-5D-5L.mp. or European Quality of Life-5 Dimension* 5 Level*.mp. or EuroQ?ol 5D-5L.mp. or EuroQuol 5 Dimension* 5 Level*.mp.

28. Asthma Control Test*.mp. or Asthma Control Test/ or ACT.mp.

29. Asthma Control questionnaire*.mp. or Asthma Control Questionnaire/ or ACQ.mp.

30. (Childhood Asthma control test* or CACT or C-ACT).mp.

31. ((Asthma Control and Communication Instrument) or ACCI).mp.

32. (Breathmobile Assessment of Asthma Control or Breathmobile).mp.

33. Asthma Control in Children.mp.

34. ((Seattle Asthma Severity and Control Questionnaire*) or SASCQ).mp.

35. (Lara Asthma Symptom Scale or LASS).mp.

36. (P?ediatric Asthma Control Tool or PACT).mp.

37. (Functional Severity of Asthma Scale or FSAS).mp.

38. (Asthma Control Scoring System or ACSS).mp.

39. 30-Second Asthma Test*.mp.

40. Asthma Quiz.mp.

41. (Pictorial Quality of Life Measure for Young Children With Asthma or Pictorial PAQLQ).mp.

42. P?ediatric Asthma Quality of Life Questionnaire*.mp.

43. pictorial.mp.

44. 42 and 43

45. (Asthma Symptom Utility Index or ASUI).mp.

46. (P?ediatric asthma diary or PAD).mp.

47. (Total asthma symptoms scores or TASS).mp.

48. (Symptom Free day* questionnaire* or SFDQ).mp.

49. (Asthma Symptom Diary or ASD).mp.

50. (daytime and nocturnal asthma symptom diary scale*).mp.

51. (Physician Severity Rating Scale or PSRS).mp.

52. Standardized Measure to Assess Response to Therapy.mp.

53. (Global Initiative for Asthma questionnaire* or GINAQ).mp.

54. (Composite asthma severity index or CASI).mp.

55. hospitali?ation*.mp. or hospitalization/

56. adverse drug reaction/ or drug safety/ or adverse reaction*.mp. or adverse event.mp. or adverse event/

57. prednisolone.mp. or prednisolone/

58. corticosteroid therapy/ or corticosteriod*.mp. or OCS*.mp.

59. exacerbation*.mp. or disease exacerbation/

60. (P?ediatric Asthma Symptom Diary Scale or PASDS).mp.

61. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60

62. ((patient* or consumer*) adj3 (decisi* or decid*)).mp.

63. consumer satisfaction/ or patient satisfaction/ or consumer satisfaction.mp.

64. exp patient preference/ or exp patient attitude/

65. ("patient-focused" or "patient-centered" or "patient-centred" or patient reported or "patient satisfaction").mp.

66. (patient experience or patient understanding).mp.

67. (patient acceptance or informed choice).mp. or exp shared decision making/ or clinical decision making/ or exp patient decision making/ or shared decision making.mp. or clinical decision making.mp. or patient decision making.mp. or self management.mp. or patient comfort/

68. patient* need*.mp.

69. ((patient* or consumer* or parent* or child* or adolescent* or caregiver* or carer* or guardian* or famil* or spouse*) adj3 (opinion* or attitude* or desir* or perspective* or view* or preference* or perception*)).mp.

70. emotion/ or exp affect/ or exp anger/ or exp disgust/ or exp fear/ or anxiety/ or exp frustration/ or exp happiness/ or exp helplessness/ or exp hope/ or exp nervousness/ or exp patient worry/ or exp unhappiness/ or emotion*.mp. or affect*.mp. or anger.mp. or angry.mp. or disgust*.mp. or fear.mp. or anxiety.mp. or anxious.mp. or frustration.mp. or frustrated.mp. or happiness.mp. or happy.mp. or helpless*.mp. or hope*.mp. or nervous*.mp. or worry.mp. or worried.mp. or unhappiness.mp. or unhappy.mp. or Dissatisfaction.mp. or Disappointment.mp. or Doubt.mp.

71. ((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire*)) or ("focus group*" or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).ti,ab. or survey*.mp.

72. exp interview/ or information processing/ or thematic analysis/ or verbal communication/ or qualitative research/ or qualitative analysis/

73. 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70

74. 71 or 72

75. letter/ or editorial/ or review/ or case report/ or case report*.mp. or editorial*.mp. or letter*.mp.

76. (conference abstract* or conference paper*).mp. or exp conference paper/ or exp conference abstract/ or exp "conference review"/ or exp symposium/ or exp workshop/

77. ((systematic or narrative) adj2 review*).mp. or "systematic review"/

78. exp animal model/ or exp biological model/ or exp avian model/ or exp bovine model/ or exp canine model/ or exp caprine model/ or exp equine model/ or exp feline model/ or exp fish model/ or exp frog model/ or exp fruit fly model/ or exp invertebrate model/ or exp nematode model/ or exp ovine model/ or exp porcine model/ or exp primate model/ or exp rabbit model/ or exp rodent model/

79. exp model/ or exp adverse outcome pathway/ or exp anatomic model/ or exp biological model/ or exp disease model/ or exp experimental model/ or exp genetic model/ or exp information model/ or exp lung model/ or exp membrane model/ or exp molecular model/ or exp nonbiological model/ or exp population model/ or exp process model/ or exp simulation/ or exp structural model/ or exp theoretical model/

80. exp mouse/ or exp murine/ or exp experimental mouse/ or exp mus booduga/ or exp mus musculus/ or exp mus spretus/ or exp mus terricolor/

81. (canine* or dog* or feline* hamster* or lamb* or mice or monkey* or mouse or murine or pig* or piglet* or porcine* or primate* or rabbit* or rat* or rodent* or sheep*).mp.

82. 75 or 76 or 77 or 78 or 79 or 80 or 81

83. 3 and 61 and 73 and 74

84. 83 not 82

85. 84 not ((exp animal/ or nonhuman/) not exp human/)

86. limit 85 to english language

87. limit 86 to yr="2000 -Current"

II. 'Your views about the tools used to understand asthma better': a Pan-European survey

1. Introduction

A cross-sectional survey was conducted to understand patients' and carers' views from across Europe about outcome measures used for asthma. It was approved by the University of Southampton ethics committee (ERGO:56181).

2. Methods

2.1 The questionnaire

The questionnaire was developed by 3TR researchers and members of the adult and youth 3TR Patient Working Groups (PWG). The survey was pilot-tested on a sample representative of the target population to ensure clarity and understanding as well as the time required to complete the survey, which was approximately 15 minutes.

The anonymised survey included 28 questions and was divided between 8 questions about demographic information (patient or parent/carer, severe asthma, age, gender, education, country) and 20 questions about outcome measures for severe asthma: questionnaires, breathing tests, sputum tests and blood tests. Apart from multiple choice questions, participants were asked to rank the level of importance of certain characteristics of questionnaires and tests using a 5-point scale: 1 "Not important," to 5 "Very Important," plus a "No opinion" option was available. Options for free-text responses were provided. At the end of the survey, participants were asked to choose five outcomes and then rank them in order of importance.

2.2 Participants and data collection

We invited patients aged 11 years and above with severe asthma as well as parents or carers of patients with severe asthma 6 years of age or above. Severe asthma was defined according to the modified American Thoracic Society and European Respiratory Society (ATS/ERS) statement[9]. The survey was translated by a translation agency and volunteers into 14 different languages including Dutch, French, German, Italian, Polish, Czech, Swedish, Danish, Portuguese, Russian, Spanish, Turkish, and Bulgarian. The link to the survey in SurveyMonkey was disseminated through the ELF and EFA websites, newsletters, and websites of patient organisations across Europe, 3TR PWG members' networks and social media (Twitter, Facebook). Before accessing the questionnaire, potential respondents were informed about the survey's purpose, the organisations conducting the survey and the average time required to complete. The survey was conducted between 26th November 2020 and 13th January 2021.

2.3 Qualitative analysis

All free-text comments from patients with severe asthma and their parents/carers were analysed using qualitative analysis. Comments in languages other than English were translated by the translator agency and volunteers. Braun and Clarke's steps for thematic analysis were used for analysis.[10] Each comment was coded in duplicate (EK, AR) and the codes were then combined into themes. Any discrepancies were resolved through discussion and, if necessary, a third reviewer (GR) was consulted.

3. Results

3.1 Table S2. Characteristics of respondents for the pan-European survey.

	Patient	Parent or carer
Number of patients, n (%)	201 (86.6)	31 (13.4)
Gender, n (%)		
Female	154 (76.6)	27 (87.1)
Male	44 (21.9)	4 (12.9)
Prefer not to say	2 (1.0)	0 (0.0)
Other	1 (0.5)	0 (0.0)
Highest level of education, n (%)		
Still in school	4 (2.0)	5 (16.1)
Completed school	17 (8.5)	1 (3.2)
Junior college/vocational training	56 (27.9)	2 (6.5)
University/college	118 (58.7)	22 (71.0)
Prefer not to say	6 (3.0)	1 (3.2)
Characteristics of severe asthma, n (%)*		
three or more courses of steroid tablets	83 (41.3)	13 (41.9)
daily or every other day treatment with steroid tablets	78 (38.8)	10 (32.3)
treatment with a biological drug	111 (55.2)	15 (48.4)
an emergency hospital admission due to asthma in previous year	60 (29.9)	7 (22.6)
Duration of severe asthma, years (median, IQR)	12 (5-29)	7 (4-15)
Country		
UK	65 (32.3)	1 (3.2)
Italy	48 (23.9)	1 (3.2)
Germany	36 (17.9)	4 (12.9)
Russia	15 (7.5)	9 (29.0)
Spain	10 (5.0)	5 (16.1)
Sweden	8 (4.0)	1 (3.2)
Netherlands	6 (3.0)	1 (3.2)
Others**	13 (6.5)	9 (29.0)

* Severe asthma was defined according to the modified American Thoracic Society and European Respiratory Society (ATS/ERS) statement 2014.

** Data presented as number of patient/parent or carer: Austria (n=2;n=0); Belgium (n=0;n=1); Bulgaria (n=0;n=1);France (n=0;n=1); Greece (n=0;n=2); Hungary (n=1;n=0); Iceland (n=0;n=1); Ireland (n=3;n=0); Norway (n=1;n=0); Poland (n=3;n=1); Portugal (n=1;n=0); Switzerland (n=1;n=0); Turkey (n=2;n=1); Ukraine (n=0;n=1).

3.2 Results about questionnaires and scales for asthma.

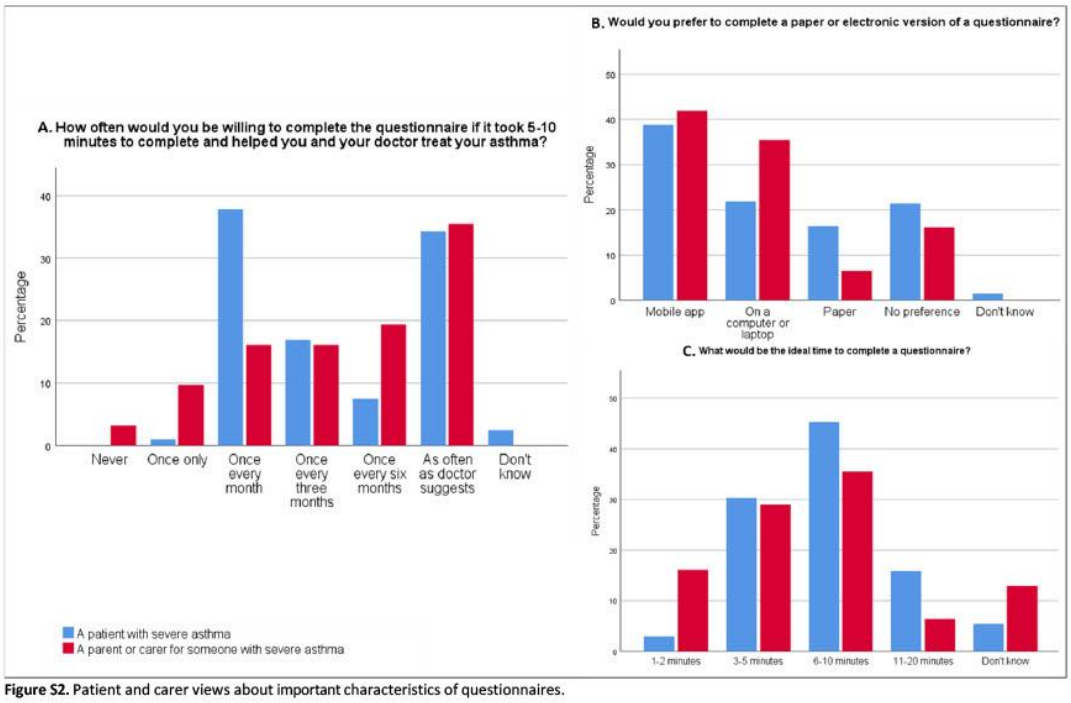


Figure S2. Patient and carer views about important characteristics of questionnaires.

Table S3. Patient and carer views about important characteristics of questionnaires.

Theme	Number of comments*	Quotes
• Questions about quality of life, including impact onself (physical and emotional), family and social relationships, and work	++++	*"... also consider including other aspects of health and life that severe asthma affects eg anxiety and depression levels, pain levels etc."*
• Easy to understand instructions, questions,response options and results	++++	*"Make it easy enough to understand how it works but not patronising eg don't use smiley faces!"*
• Questionnaires tailored to target population (adult vs child) / individual patient o Questionnaire should capture the diversity of different forms of asthma, individual patient and between patient variability. For example, seasonal or time of day variation. o Questions should be relevant to patient	++ +++ ++	*"Able if possible to capture variability. I struggle with current questionnaires because they fail to capture eg that some days I needed no reliever and other days needed a lot."* *"The frequency of the questionnaires has to be relevant for the disease course of an individual patient."*
• Questions about effectiveness / side effects ofprevious and current medication (including biological therapy)	+++	*"Questions about pain, interactions with other medications, secondary diseases caused by asthma or medication, tolerance of medication."*
• Response options should cover a broad range and be differentiated enough to capture a patient's condition o Questionnaire should include comment field	+ +++	*"Places to put my own comment as everyone's different and don't all fit in a box."* *"I would like space to be able to add comments/extra info on questions as not all answers are simple!"*

• Discussion with doctor to understand meaning of test results o Questionnaire completion should lead to 'action'/change in patient's care	++ +	*"If the questionnaires are relevant and something is done with the answers, thet time is of less importance."*
• Questions about pain levels / symptoms /experience/ triggers of exacerbations	++	*"Consider including other aspects of health and life that severe asthma affects eg pain levels etc."*
• Questions should be related to clinical tests e.g.lung function, FeNO	++	*"The asthma control test questions are not differentiated enough and do not have a sufficient link to formulations and daily peak flow value criteria. That frustrates me every time I fill in the ACT questionnaire..."*
• Willing to complete questionnaire as often as necessary	+	*"Feel free to fill in a questionnaire daily morning and evening if it helps with my asthma"*
• Online record e.g. app (linked to specialist) of patients test results, including questionnaire results, breath test results, pulse oximeter, symptoms o Easy to access e.g. asthma diary in an app	+ +	*"I think an app that links up to specialist with PF, symptoms and other information."*
• Recall period should be longer than 2 weeks	+	*"...more questions than the current ACQ & over a longer duration. Consultant appointments are only every few months & looking at symptoms over last 2 weeks isn't reflective."*

*Pluses are based on the number of comments: 1-5 (+); 6-10 (++); 11-15 (+++); ≥16 (++++). ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; FeNO, Exhaled Nitric Oxide.

3.3. Results about clinical tests used for assessing severe asthma.

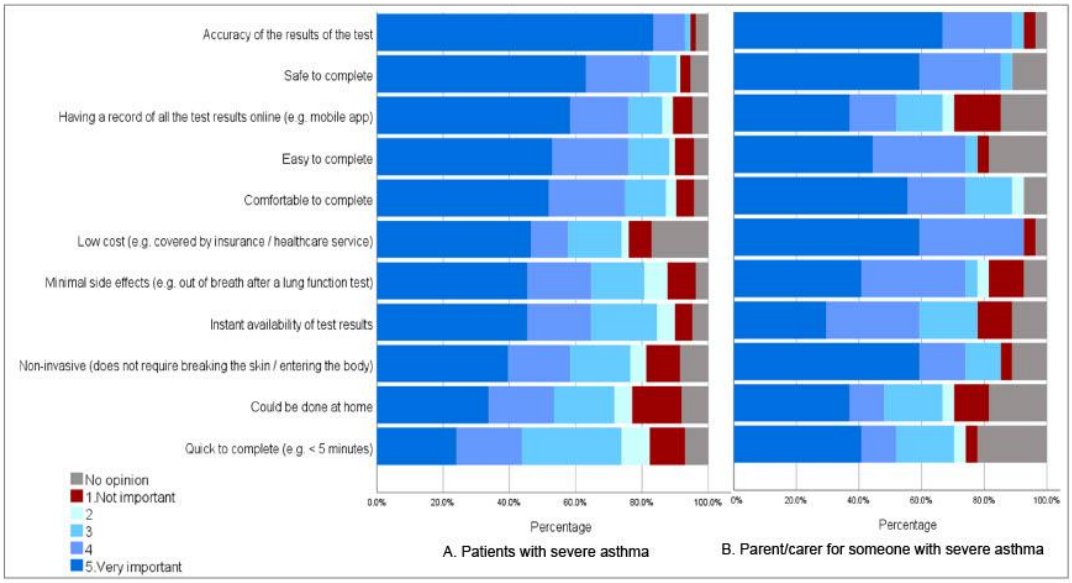


Figure S3. Patient and carer views about characteristics of clinical tests.

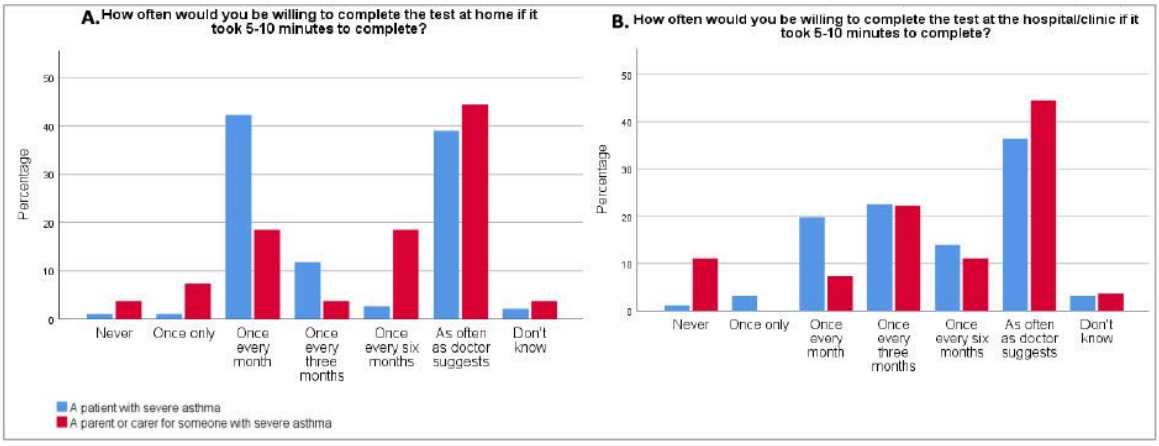


Figure S4. Patient and carer views about ease of completion of lung function tests.

Table S4. Patient and carer views about characteristics of lung function tests.

Theme	Number of comments*	Quotes
• Explanation of test purpose/results/clear instructions/ questions/ easy to understand results	+++	*"A good explanation is given for the measures and there is a clear purpose."*
○ Test should be easy/quick to perform	++	
• Test should be sensitive enough to capture any changes in patient's condition, and reproducible/consistent	+	*"They must acknowledge variability - good days/bad days and also that tests can be normal but there is still severe asthma"*
• Should capture different aspects of (severe) asthma, and intra- and inter-patient variability	+++	
• Willing to perform test as often as needed if understand purpose of test / leads to better care	+	*"Sometimes tests aren't nice to do or easy and can make you breathless but they are necessary"*
• Completing test should lead to identifiable output	+	
• Discussion with doctor about meaning (and limitations) oftest results	++	*"Medical professionals to tell me the results and explain what they mean and the implications for my asthma. I am very interested and what to know more."*
• Remote testing is convenient/ provides realistic picture of patient's condition/ can be done repeatedly	++	*"At home tests more regularly can find a better picture than one off tests at hospital"*
• Should be safe to perform	+	*"That they are easy to access and have no risks"*
○ Need painless tests	+	
• Objective tests provide a snapshot but are not reflective of the patient's long-term condition	+	*"I have had situations where they rely solely on a lung function test which takes a narrow snapshot of what is happening and do NOT listen (and actively dismiss) any recent or long term history so miss patterns."*

• Tests should assess chest tightness and breathlessness	+	*"the chest tightness of my child and being out of her/his breath"*
• Availability of test results via app	+	*"Analyses/comparisons with previous values are clear and easy for the patient to understand e.g. via the app."*

*Pluses are based on the number of comments: 1-5 (+); 6-10 (++); 11-15 (+++); ≥16 (++++).

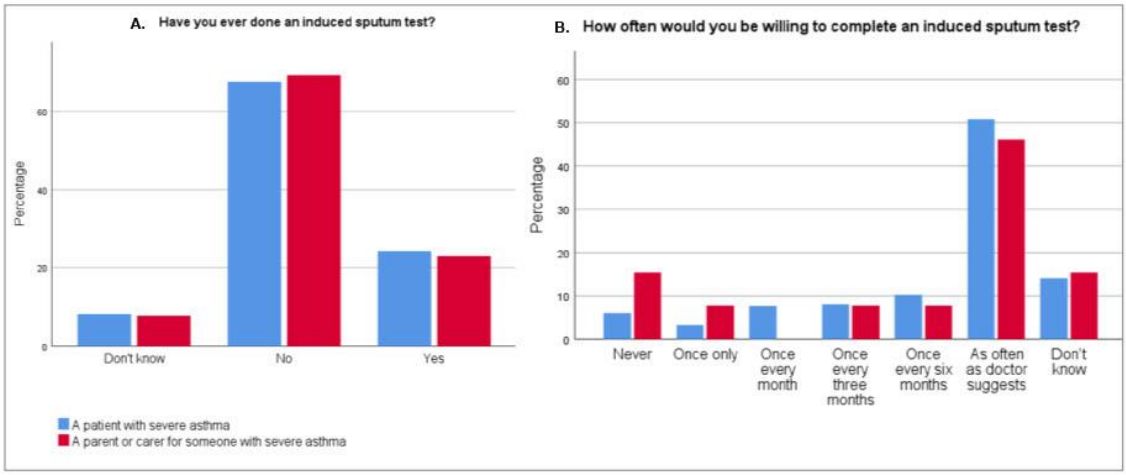


Figure S5. Patients and carer views about induced sputum testing.

Table S5. Patient and carer views about induced sputum testing.

Theme	Number of comments*	Quotes
• Induced sputum testing is associated with discomfort. Often seen as a frustrating / unpleasant experience/not willing to do it	++	*"it's very annoying and irritating, I've done it several times but I prefer not to have to do it again"*
o Frustrating/challenging for patients who find it difficult to cough up sputum	+	*"Not all patients may be able to carry out this test (if they don't produce sputum)!"*
• Never heard of / done it	++	*"Not done one but what I've heard makes me think I wouldn't want it to be regular."*
• Procedure needs to be optimized (salty solution not always effective, ways to soften mucus)	+	*"any medication that can soften the mucus"*
o Should be made painless, and less invasive	+	
• Unsafe/post-test monitoring required	+	*"There must be good guidance for administration and coping with the consequences."*
• Guidance on coping with consequences	+	
o Need clear instructions for performing test	+	
o Prefer if done at specialist hospital	+	
o Discussion with doctor about meaning of test results	+	
• At home testing	+	*"Find a way to do it at home regularly. This would have been particularly useful for me at times when the doc really should be getting a sample of it to test."*
o Test should be easy to access/local	+	
• Willing to perform as often as necessary	+	*"It depends on how and the consequences, but as often as necessary. There must be good guidance for administration and coping with the consequences. As often as relevant to me as a patient."*

• Test not meaningful	+	*"Was frustrated and not meaningful"*
○ Clinical tests are snapshot, not always reflective of overall patient condition	+	

*Pluses are based on the number of comments: 1-5 (+); 6-10 (++); 11-15 (+++); ≥16 (++++).

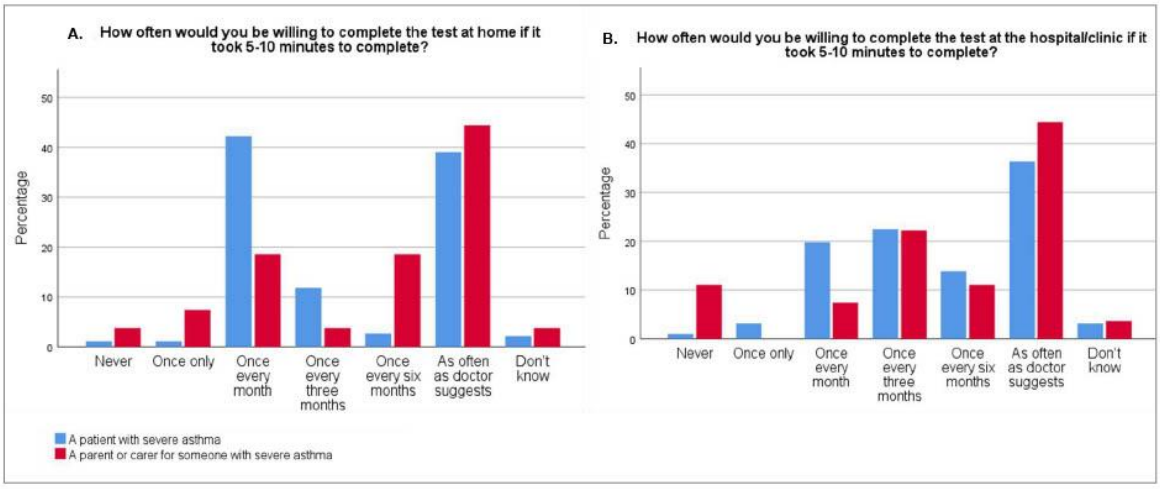


Figure S6. Patient and carer views about blood tests for assessing blood and/or sputum eosinophil count.

Table S6. Patient and carer views about blood tests to determine blood and/or sputum eosinophil counts.

Theme	Number of comments*	Quotes
• Would prefer at home blood tests	++	*"A home test system as diabetics have, would be ideal"*
• Discussion with doctor to understand meaning of test results	++	*"I want to be told the results, even if normal and what the results mean."*
• Discomfort/ stressful experience/ want to do as less times as possible	+	*"As less blood tests as possible. It results in stress and is difficult to handle as you are already severely ill (dyspnoeic)"*
• Willing to do as many times as necessary o Test(s) should be done based on doctor's recommendation	+ +	*"I don't mind having bloods when I have my biologic. I wouldn't want to go to hospital for a blood test. My specialist hospital is 2hrs away. When I go I want it to be useful."*
• Allows comparison between effects of individual medications	+	*"It makes a comparison between the effects of individual medications."*
• Test is not valuable/ not good at capturing severity/no relationship between blood tests and airway activity for non-eosinophilic asthma	+	*"Kind of depends what they're measuring. I would be willing to do it more often if I knew they had a reliable relationship with what's happening in my airways (I have non-eosinophilic asthma and feel my consultant places too much reliance on blood tests which don't really tell him enough)."*
• Not always possible/ feasible to do e.g. if patient has poor veins	+	*"Not an option if you have poor veins."*
• Need combination of tests, not only blood test o Lab / clinical tests provide snapshot, not always reflective of overall patient condition	+ +	*"The view has to be broader that only blood tests"* *"Current tests often just look at the "numbers", but the illness is more than just a sick pair of lungs."*

*Pluses are based on the number of comments: 1-5 (+); 6-10 (++); 11-15 (+++); ≥16 (++++)

III. Results of multi-round online voting to select COM set for severe asthma

1. Adult COM set for severe asthma

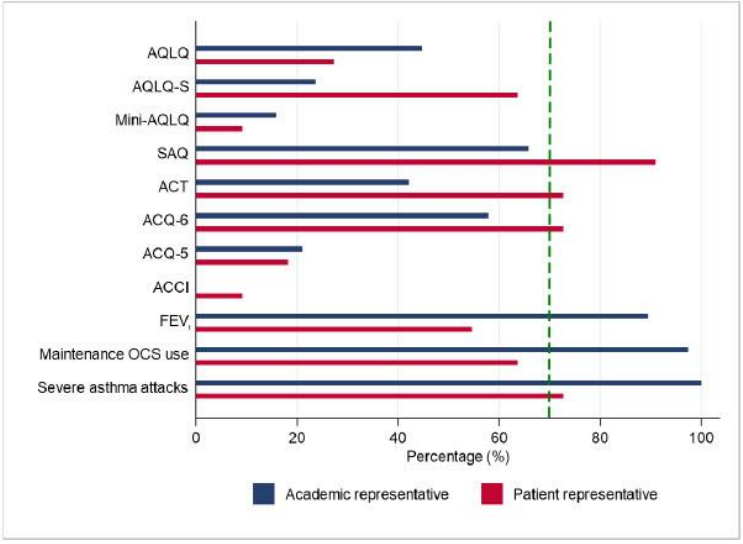


Figure S7. Outcome measures ranked in round 1 by academic and patient representatives.

Academic group included clinicians, researchers, pharmaceutical and regulatory representatives. AQLQ, Asthma Quality of Life Questionnaire; AQLQ-S, Asthma Quality of Life Questionnaire Standardised; Mini-AQLQ, Mini Asthma Quality of Life Questionnaire; SAQ, Severe Asthma Questionnaire; ACT, Asthma Control Test; ACQ-6, Asthma control questionnaire 6 (symptoms and rescue medication use); ACQ-5, Asthma control questionnaire 5 (symptoms only); ACCI, Asthma control and communication instrument; FEV_1, Forced expiratory volume in 1 second; OCS, Oral Corticosteroid.

Table S7. Outcome measures ranked in round 1 by stakeholder groups.

	Clinician and researcher n (%)	Patient representative n (%)	Pharmaceutical representative n (%)	Health regulator n (%)
Questionnaires to assess quality of life				
Asthma Quality of Life Questionnaire (AQLQ)	12 (40.0)	3 (27.3)	1 (33.3)	4 (80.0)
Asthma Quality of Life Questionnaire Standardised (AQLQ-S)	8 (26.7)	7 (63.6)	1 (33.3)	0 (0.0)
Mini Asthma Quality of Life Questionnaire (Mini-AQLQ)	6 (20.0)	1 (9.1)	0 (0.0)	0 (0.0)
Severe Asthma Questionnaire (SAQ)	19 (63.3)	10 (90.9)	1 (33.3)	5 (100.0)
Questionnaires to assess asthma control				
Asthma Control Test (ACT)	14 (46.7)	8 (72.7)	2 (66.7)	0 (0.0)
Asthma control questionnaire 6 *(symptoms + rescue medication use)* (ACQ-6)	15 (50.0)	8 (72.7)	3 (100.0)	4 (80.0)
Asthma control questionnaire 5 *(symptoms only)* (ACQ-5)	8 (26.7)	2 (18.2)	0 (0.0)	0 (0.0)
Composite outcome measures				
Asthma control and communication instrument (ACCI)	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)
Clinical outcome measures				
Forced expiratory volume in 1 second (FEV_1)	26 (86.7)	6 (54.5)	3 (100.0)	5 (100.0)
Healthcare resource use measures				
Maintenance Oral Corticosteroid (OCS) use	29 (96.7)	7 (63.6)	3 (100.0)	5 (100.0)
Severe asthma attacks *(severe exacerbations)*	30 (100.0)	8 (72.7)	3 (100.0)	5 (100.0)

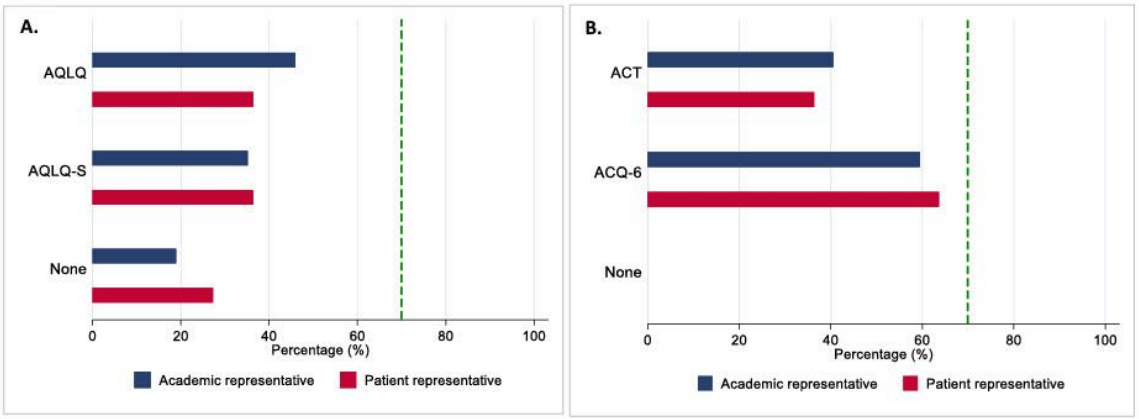


Figure S8. Outcome measures ranked in round 2 by academic and patient representatives.

A. Ranking quality of life instruments for extended core outcome measures set (COM-E). B. Ranking asthma control instruments. Academic group included clinicians, researchers, pharmaceutical and regulatory representatives. AQLQ, Asthma Quality of Life Questionnaire; AQLQ-S, Asthma Quality of Life Questionnaire Standardised; ACT, Asthma Control Test; ACQ-6, Asthma control questionnaire 6 (symptoms and rescue medication use).

Table S8. Outcome measures ranked in round 2 by stakeholder groups.

	Clinician and researcher n (%)	Patient representative n (%)	Pharmaceutical representative n (%)	Health regulator n (%)
Choosing between ACT and ACQ-6				
Asthma Control Test (ACT)	12 (38.7)	4 (36.4)	1 (100.0)	1 (25.0)
Asthma control questionnaire 6 *(symptoms + rescue medication use)* (ACQ-6)	19 (61.3)	7 (63.6)	-	3 (75.0)
None	-	-	-	-
Can the AQLQ or the AQLQ-S fit in our Core Outcome Set?				
Asthma Quality of Life Questionnaire (AQLQ)	13 (41.9)	4 (36.4)	-	4 (100.0)
Asthma Quality of Life Questionnaire Standardised (AQLQ-S)	11 (35.5)	4 (36.4)	1 (100.0)	-
None	7 (22.6)	3 (27.3)	-	-

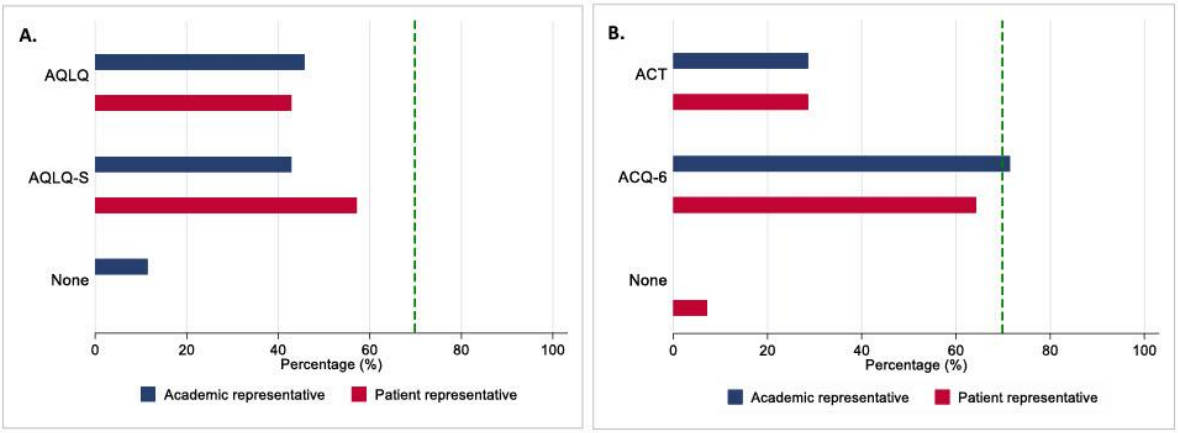


Figure S9. Outcome measures ranked in round 3 by academic and patient representatives.

A. Ranking quality of life instruments for extended core outcome measures set (COM-E). B. Ranking asthma control instruments. Academic group included clinicians, researchers, pharmaceutical and regulatory representatives. AQLQ, Asthma Quality of Life Questionnaire; AQLQ-S, Asthma Quality of Life Questionnaire Standardised; ACT, Asthma Control Test; ACQ-6, Asthma control questionnaire 6 (symptoms and rescue medication use).

Table S9. Outcome measures ranked in round 3 by stakeholder groups.

	Clinician and researcher n (%)	Patient representative n (%)	Pharmaceutical representative n (%)	Health regulator n (%)
Choosing between ACT and ACQ-6				
Asthma Control Test (ACT)	7 (26.9)	4 (29.6)	2 (50.0)	1 (20.0)
Asthma control questionnaire 6 *(symptoms + rescue medication use)* (ACQ-6)	19 (73.1)	9 (64.3)	2 (50.0)	4 (80.0)
None	-	-	-	-
Can the AQLQ or the AQLQ-S fit in our Core Outcome Set?				
Asthma Quality of Life Questionnaire (AQLQ)	11 (42.3)	6 (42.9)	1 (25.0)	4 (80.0)
Asthma Quality of Life Questionnaire Standardised (AQLQ-S)	12 (46.2)	8 (57.1)	3 (75.0)	-
None	3 (11.5)	-	-	1 (20.0)

2. Paediatric COM set for severe asthma

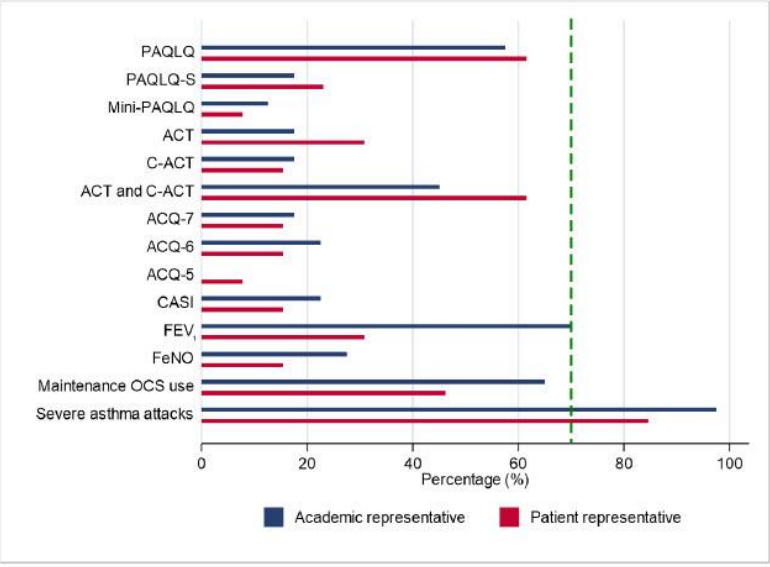


Figure S10. Outcome measures ranked in round 1 by academic and patient representatives.

Academic group included clinicians, researchers, pharmaceutical and regulatory representatives. PAQLQ, Paediatric Asthma Quality of Life Questionnaire; PAQLQ-S, Paediatric Asthma Quality of Life Questionnaire Standardised; Mini-PAQLQ, Mini Paediatric Asthma Quality of Life Questionnaire; ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Test; ACQ, Asthma Control Questionnaire; ACQ-7: questions about symptom control, rescue medication use, and forced expiratory volume in 1 second (FEV_1); ACQ-6: questions about symptom control, and rescue medication use; ACQ-5: questions about symptom control only; CASI, Composite Asthma Severity Index; FEV_1, Forced expiratory volume in 1 second; FeNO, Fractional exhaled nitric oxide; OCS, Oral Corticosteroid.

Table S10. Outcome measures ranked in round 1 by stakeholder groups.

	Clinician and researcher n (%)	Patient representative n (%)	Pharmaceutical representative n (%)	Health regulator n (%)
Questionnaires to assess quality of life				
Paediatric Asthma Quality of Life Questionnaire (PAQLQ)	20 (55.6)	8 (61.5)	-	3 (100.0)
Paediatric Asthma Quality of Life Questionnaire Standardised (PAQLQ-S)	6 (16.7)	3 (23.1)	1 (100.0)	-
Mini Paediatric Asthma Quality of Life Questionnaire (Mini-PAQLQ)	5 (13.9)	1 (7.7)	-	-
Questionnaires to assess asthma control				
Asthma Control Test (ACT) [for ≥12 years]	7 (19.4)	4 (30.8)	-	-
Childhood Asthma Control Test (C-ACT) [for children 4-11 years, and carers]	7 (19.4)	2 (15.4)	-	-
Asthma Control Test (ACT) [for ≥12 years] AND Childhood Asthma Control Test (C-ACT) [for children 4-11 years, and carers]	17 (47.2)	8 (61.5)	-	1 (33.3)
Asthma control questionnaire 7 *(symptoms, rescue medication use + FEV_1)* (ACQ-7)	6 (16.7)	2 (15.4)	1 (100.0)	-
Asthma control questionnaire 6 *(symptoms + rescue medication use)* (ACQ-6)	7 (19.4)	2 (15.4)	-	2 (66.7)
Asthma control questionnaire 5 *(symptoms only)* (ACQ-5)	-	1 (7.7)	-	-
Composite outcome measures				
Composite Asthma Severity Index (CASI)	9 (25.0)	2 (15.4)	-	-
Clinical outcome measures				
Forced expiratory volume in 1 second (FEV_1)	24 (66.7)	4 (30.8)	1 (100.0)	3 (100.0)
Fractional exhaled nitric oxide (FeNO)	11 (30.6)	2 (15.4)	-	-
Healthcare resource use measures				
Maintenance Oral Corticosteroid use	22 (61.1)	6 (46.2)	1 (100.0)	3 (100.0)
Severe asthma attacks *(severe exacerbations)*	35 (97.2)	11 (84.6)	1 (100.0)	3 (100.0)

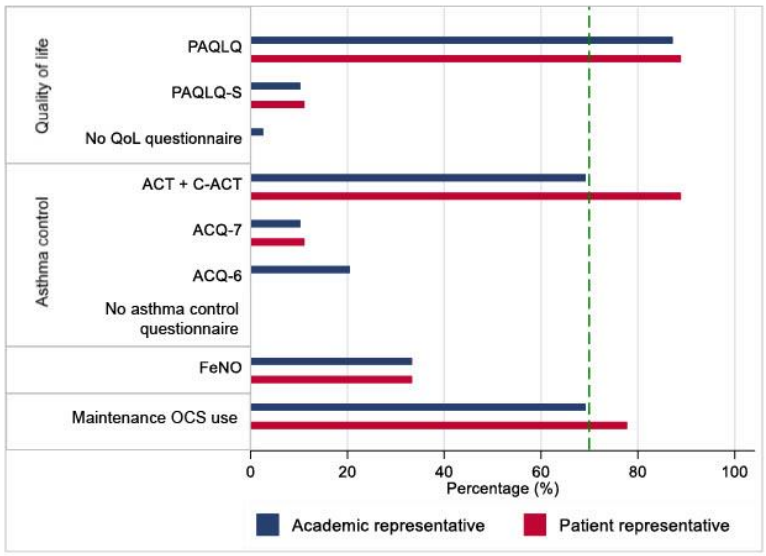


Figure S11. Outcome measures ranked in round 2 by academic and patient representatives.

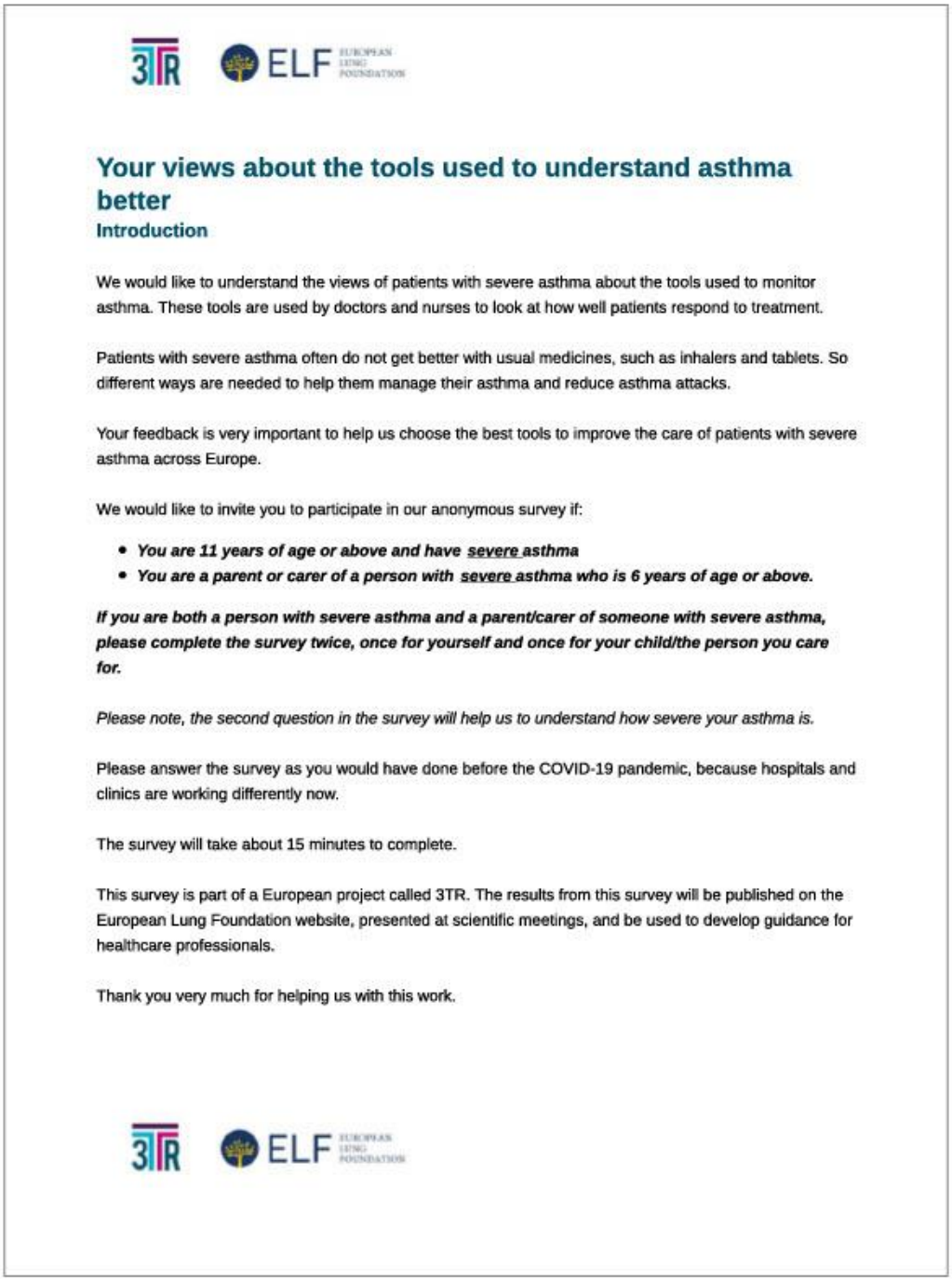
Academic group included clinicians, researchers, pharmaceutical and regulatory representatives. PAQLQ, Paediatric Asthma Quality of Life Questionnaire; PAQLQ- S, Paediatric Asthma Quality of Life Questionnaire Standardised; QoL, Quality of Life; ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Test; ACQ, Asthma Control Questionnaire; ACQ-7: questions about symptom control, rescue medication use, and forced expiratory volume in 1 second (FEV_1); ACQ-6: questions about symptom control, and rescue medication use; FeNO, Fractional exhaled nitric oxide; OCS, Oral Corticosteroid.

Table S11. Outcome measures ranked in round 2 by stakeholder groups.

	Clinician and researcher n (%)	Patient representative n (%)	Pharmaceutical representative n (%)	Health regulator n (%)
Questionnaires for quality of life				
Paediatric Asthma Quality of Life Questionnaire (PAQLQ)	30 (88.2)	8 (88.9)	1 (50.0)	3 (100.0)
Paediatric Asthma Quality of Life Questionnaire Standardised (PAQLQ-S)	3 (8.8)	1 (11.1)	1 (50.0)	-
No quality of life questionnaire	1 (2.9)	-	-	-
Questionnaires for asthma control				
Asthma Control Test (ACT) [for ≥12 years] AND Childhood Asthma Control Test (C-ACT) [for children 4-11 years, and carers]	27 (79.4)	8 (88.9)	-	-
Asthma control questionnaire 7 *(symptoms, rescue medication use + FEV_1)* (ACQ-7)	3 (8.8)	1 (11.1)	1 (50.0)	-
Asthma control questionnaire 6 *(symptoms + rescue medication use)* (ACQ-6)	4 (11.8)	-	1 (50.0)	3 (100.0)
Clinical outcome measures				
Fractional exhaled nitric oxide (FeNO)	11 (32.4)	3 (33.3)	2 (100.0)	-
Healthcare resource use measures				
Maintenance Oral Corticosteroid (OCS) use	22 (64.7)	7 (77.8)	2 (100.0)	3 (100.0)

IV. Copy of the pan-European survey: 'Your views about the tools used to understand asthma better'

Please find below the patient version of the survey. Please note that parent/carer version was also available for the relevant responders.



Your views about the tools used to understand asthma better

Introduction

We would like to understand the views of patients with severe asthma about the tools used to monitor asthma. These tools are used by doctors and nurses to look at how well patients respond to treatment.

Patients with severe asthma often do not get better with usual medicines, such as inhalers and tablets. So different ways are needed to help them manage their asthma and reduce asthma attacks.

Your feedback is very important to help us choose the best tools to improve the care of patients with severe asthma across Europe.

We would like to invite you to participate in our anonymous survey if:

- ***You are 11 years of age or above and have severe asthma***
- ***You are a parent or carer of a person with severe asthma who is 6 years of age or above.***

If you are both a person with severe asthma and a parent/carer of someone with severe asthma, please complete the survey twice, once for yourself and once for your child/the person you care for.

Please note, the second question in the survey will help us to understand how severe your asthma is.

Please answer the survey as you would have done before the COVID-19 pandemic, because hospitals and clinics are working differently now.

The survey will take about 15 minutes to complete.

This survey is part of a European project called 3TR. The results from this survey will be published on the European Lung Foundation website, presented at scientific meetings, and be used to develop guidance for healthcare professionals.

Thank you very much for helping us with this work.

Your views about the tools used to understand asthma better

General information about you to help us understand your answers

*** Q1. Are you:**

- a patient with asthma
- a parent or carer for someone with asthma
- neither of the above

Your views about the tools used to understand asthma better

General information about you to help us understand your answers

*** Q2. This question helps us to understand your asthma. During the last year I had (please tick all options that apply):**

- three or more courses of steroid tablets such as prednisone, prednisolone or cortisone
- daily or every other day treatment with steroid tablets such as prednisone, prednisolone or cortisone
- treatment with a biological drug by injection such as omalizumab [Xolair], mepolizumab [Nucala], reslizumab [Cinquero], benralizumab [Fasenra], or dupilumab [Dupixent]
- an emergency hospital admission due to asthma
- none of the above
- don't know

Q3. If none of the options above apply to you, please provide more information about your asthma medication, including the dose and the number of puffs or tablets that you take every day. (Maximum of 30 words)

*** Q4. How long have you had severe asthma? Please type in the number of years.**

*** Q5. How would you identify your gender?**

- Female
- Male
- Other
- Prefer not to say

*** Q6. What is your age group?**

- 11 – 13
- 14 – 17
- 18 – 20
- 21 – 29
- 30 – 39
- 40 – 49
- 50 – 59
- 60 – 70
- 71 – 80
- 81 or above

*** Q7. What is the highest level of education you have completed?**

- Still in school
- Completed school
- Junior college/vocational training
- University/college
- Prefer not to say

*** Q8. In what country do you live?**

Your views about the tools used to understand asthma better

Questions about tools for severe asthma

The questions in this section are divided into groups and there will be an opportunity to provide comments.

Questionnaires

Questionnaires can help you and your doctor to understand how your asthma is affecting you. Examples are the Asthma Control Test and Asthma Quality of Life Questionnaire.

Q9. When you think about a questionnaire that your doctor might use to understand your asthma better, which characteristics are most important? *For the following questions, 1 star = not important and 5 stars = very important.*

* Questions about my asthma over a short period of time (less than 2 weeks)

No opinion


* Questions about my asthma over a long period of time (more than 2 weeks)
No opinion
* A doctor or nurse completing it with me
No opinion
* Being able to complete it on my own
No opinion
* Being able to complete it at home
No opinion
* Being able to complete it on a computer or laptop
No opinion
* Being able to complete it using a mobile app
No opinion
* Quick to complete (e.g. less than 5 minutes)
No opinion
* Accuracy of the results even if the questionnaire takes longer to complete (e.g. more than 20 minutes)
No opinion

* Answers in the form of a scale such as "0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10"

No opinion

* Answers in the form of a multiple choice, e.g. "None. A little. A lot"

No opinion

* Answers in the form of pictures, e.g. smiley face, neutral face, sad face

No opinion

* Answer in the form of "Yes/No"

No opinion

Q10. Are there any other characteristics which you think are important? (Maximum 50 words)

*** Q11. What would be the ideal time to complete a questionnaire?**

- 1-2 minutes
- 3-5 minutes
- 6-10 minutes
- 11-20 minutes
- Don't know

*** Q12. Would you prefer to complete a paper or electronic version of a questionnaire?**

- ○ On a computer or laptop
- ○ Mobile app
- ○ Paper
- ○ No preference
- ○ Don't know

*** Q13. How often would you be willing to complete the questionnaire if it took 5-10 minutes to complete and helped you and your doctor treat your asthma?**

- ○ Never
- ○ Once only
- ○ Once every month
- ○ Once every three months
- ○ Once every six months
- ○ As often as my doctor recommends
- ○ Don't know

Q14. Please add any further comments about questionnaires in order to help us to choose the best tools for severe asthma. (Maximum of 50 words)

Your views about the tools used to understand asthma better

Tests during asthma consultations / clinics

Doctors use tests at asthma consultations / clinics to assess your asthma. Examples are lung function tests or exhaled nitric oxide tests when you blow into a computer system. These tests help your doctor to best treat your asthma.

Q15. When you think about tests that your doctor uses to understand your asthma better, which characteristics are most important to you? *For the following questions, 1 star = not important and 5 stars = very important.*

* Easy to complete

No opinion

* Comfortable to complete

No opinion

* Safe to complete

No opinion

* Quick to complete (e.g. less than 5 minutes)

No opinion

* Could be done at home

No opinion

* Low cost of the test, e.g. covered by insurance or healthcare service

No opinion

* Accuracy of the results of the test

No opinion

* Non-invasive (does not require breaking the skin or entering the body)

No opinion

* Instant availability of test results

No opinion

* Having a record of all the test results online (e.g. mobile app)

No opinion

* Minimal side effects (e.g. feeling out of breath after completing a lung function test)

No opinion

Q16. Are there any other characteristics which you think are important? (Maximum of 50 words)

*** Q17. How often would you be willing to complete the test at home if it took 5-10 minutes to complete?**

- Never
- Once only
- Once every month
- Once every three months
- Once every six months
- As often as my doctor recommends
- Don't know

*** Q18. How often would you be willing to complete the test at the hospital/clinic if it took 5-10 minutes to complete?**

- Never
- Once only
- Once every month
- Once every three months
- Once every six months
- As often as my doctor recommends
- Don't know

Q19. Please enter any further comments about breathing tests to help us choose the best tools for severe asthma. (Maximum 50 words)

Your views about the tools used to understand asthma better

Induced sputum test

Your doctor may have given you a salty solution via a nebuliser to help you cough up some sputum (mucus, phlegm) from your lungs. The test is done in hospital, and it takes 30 to 60 minutes to complete. The laboratory staff measure the number of cells in the sputum. This helps the doctor to understand whether there is inflammation (swelling and redness) in the lungs and what type of inflammation is present.

*** Q20. Have you ever done an induced sputum test?**

- Yes
- No
- Don't know

*** Q21. How often would you be willing to complete an induced sputum test?**

- ○ Never
- ○ Once only
- ○ Once every month
- ○ Once every three months
- ○ Once every six months
- ○ As often as my doctor recommends
- ○ Don't know

Q22. Please enter any further comments about the induced sputum test in order to help us to choose the best tools for severe asthma. (Maximum 50 words)

Your views about the tools used to understand asthma better

Blood tests

Your doctor may have done a blood test to measure the amount and type of inflammation in your body. This helps doctors to decide which asthma medications are likely to work best for you.

*** Q23. How often would you be willing to complete a blood test at home? This might be done by you, for example using a finger prick test, or by a health professional coming to your house.**

- ○ Never
- ○ Once only
- ○ Once every month
- ○ Once every three months
- ○ Once every six months
- ○ As often as my doctor recommends
- ○ Don't know

*** Q24. How often would you be willing to complete a blood test at the hospital/clinic?**

- ○ Never
- ○ Once only
- ○ Once every month
- ○ Once every three months
- ○ Once every six months
- ○ As often as my doctor recommends
- ○ Don't know

Q25. Please enter any further comments about blood tests in order to help us to choose the best tools for severe asthma. (Maximum 50 words)

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Your views about the tools used to understand asthma better

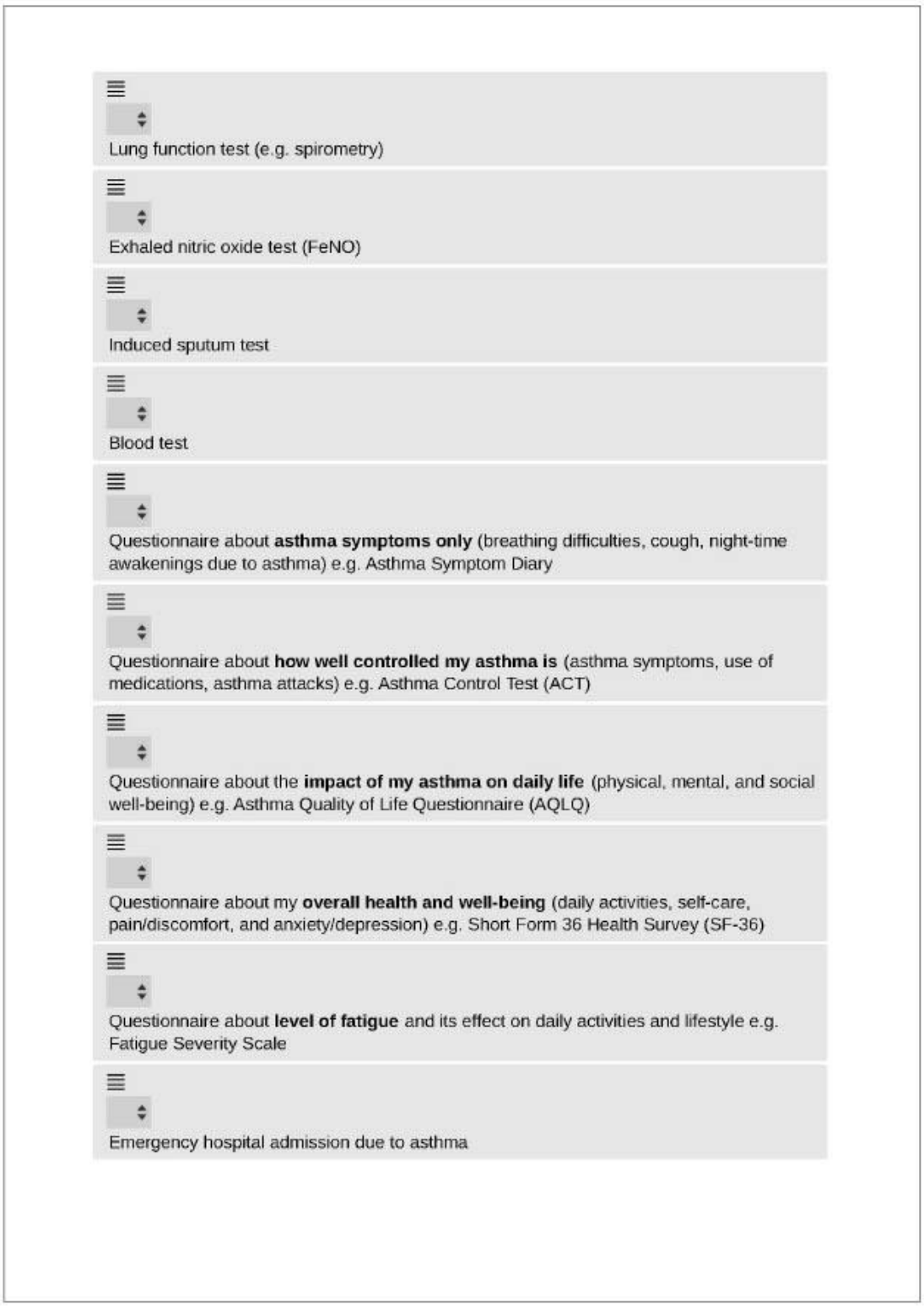
Overall view of asthma tools

*** Q26. There are lots of ways a doctor can measure how your asthma is affecting you, but it is not possible to assess all of them. We would like to understand which aspects are most important to patients so that they can be assessed in future severe asthma trials and clinical practice. Which five of the following would you prefer to be measured? (You will be able to rank them in the next question)**

- Lung function test (e.g. spirometry)
- Exhaled nitric oxide test (FeNO)
- Induced sputum test
- Blood test
- Questionnaire about **asthma symptoms only** (breathing difficulties, cough, night-time awakenings due to asthma) e.g. Asthma Symptom Diary
- Questionnaire about **how well controlled my asthma is** (asthma symptoms, use of medications, asthma attacks) e.g. Asthma Control Test (ACT)
- Questionnaire about the **impact of my asthma on daily life** (physical, mental, and social well-being) e.g. Asthma Quality of Life Questionnaire (AQLQ)
- Questionnaire about my **overall health and well-being** (daily activities, self-care, pain/discomfort, and anxiety/depression) e.g. Short Form 36 Health Survey (SF-36)
- Questionnaire about **level of fatigue** and its effect on daily activities and lifestyle e.g. Fatigue Severity Scale
- Emergency hospital admission due to asthma
- Asthma attacks
- Side effects of the medications
- Steroid tablet use (e.g. prednisolone, prednisone, cortisone)

Your views about the tools used to understand asthma better

*** Q27. Please rank the tools in order of how important they are to you.**


Lung function test (e.g. spirometry)
Exhaled nitric oxide test (FeNO)
Induced sputum test
Blood test
Questionnaire about **asthma symptoms only** (breathing difficulties, cough, night-time awakenings due to asthma) e.g. Asthma Symptom Diary
Questionnaire about **how well controlled my asthma is** (asthma symptoms, use of medications, asthma attacks) e.g. Asthma Control Test (ACT)
Questionnaire about the **impact of my asthma on daily life** (physical, mental, and social well-being) e.g. Asthma Quality of Life Questionnaire (AQLQ)
Questionnaire about my **overall health and well-being** (daily activities, self-care, pain/discomfort, and anxiety/depression) e.g. Short Form 36 Health Survey (SF-36)
Questionnaire about **level of fatigue** and its effect on daily activities and lifestyle e.g. Fatigue Severity Scale
Emergency hospital admission due to asthma

Asthma attacks

Side effects of the medications

Steroid tablet use (e.g. prednisolone, prednisone, cortisone)

Your views about the tools used to understand asthma better

Additional comments

Q28. Please add any comments which will help us better understand your answers to this survey.

Your views about the tools used to understand asthma better

Thank you.

Thank you for taking the time to complete the survey.

Researchers Kate Khaleva, Anna Rattu and Graham Roberts on behalf of the 3TR group.

Please contact Kate if you have any queries: e.khaleva@soton.ac.uk

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A4. Chapter 4. Publication 3.

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My contribution: I developed a protocol and search strategies in several databases; then I led the following: title, abstract and full-text screening; data extraction, COSMIN evaluation including risk of bias assesment and GRADE- this was done in duplicate with A. Rattu (PhD student, University of Southampton). I synthesised the evidence, drafted the tables and wrote first draft of the manuscript.

ERJ OPEN RESEARCH
REVIEW
E. KHALEVA ET AL.

Definitions of non-response and response to biological therapy for severe asthma: a systematic review

Ekaterina Khaleva [1], Anna Rattu [1], Chris Brightling [2], Andrew Bush [3], Arnaud Bourdin [4], Apostolos Bossios [5], Kian Fan Chung [6], Rekha Chaudhuri [7], Courtney Coleman [8], Ratko Djukanovic [1,9], Sven-Erik Dahlén [5], Andrew Exley [10], Louise Fleming [6], Stephen J. Fowler [11], Atul Gupta [12], Eckard Hamelmann [13], Gerard H. Koppelman [14,15], Erik Melén [16], Vera Mahler [17], Paul Seddon [18], Florian Singer [19,20], Celeste Porsbjerg [21], Valeria Ramiconi [22], Franca Rusconi [23], Valentyna Yasinska [5] and Graham Roberts [1,9] on behalf of the 3TR Asthma Definition of Response Working Group

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Shareable abstract (@ERSpublications)
There are no patient-centred composite measures of response to biologics for severe asthma. Single outcome measures are available but do not meet quality standards. A composite measure is required that is developed with patients. https://bit.ly/3FOJcXY

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Abstract

Background Biologics have proven efficacy for patients with severe asthma but there is lack of consensus on defining response. We systematically reviewed and appraised methodologically developed, defined and evaluated definitions of non-response and response to biologics for severe asthma.

Methods We searched four bibliographic databases from inception to 15 March 2021. Two reviewers screened references, extracted data, and assessed methodological quality of development, measurement properties of outcome measures and definitions of response based on COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN). A modified GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach and narrative synthesis were undertaken.

Results 13 studies reported three composite outcome measures, three asthma symptoms measures, one asthma control measure and one quality of life measure. Only four measures were developed with patient input; none were composite measures. Studies utilised 17 definitions of response: 10 out of 17 (58.8%) were based on minimal clinically important difference (MCID) or minimal important difference (MID) and 16 out of 17 (94.1%) had high-quality evidence. Results were limited by poor methodology for the

development process and incomplete reporting of psychometric properties. Most measures rated "very low" to "low" for quality of measurement properties and none met all quality standards.
Conclusions This is the first review to synthesise evidence about definitions of response to biologics for severe asthma. While high-quality definitions are available, most are MCIDs or MIDs, which may be insufficient to justify continuation of biologics in terms of cost-effectiveness. There remains an unmet need for universally accepted, patient-centred, composite definitions to aid clinical decision making and comparability of responses to biologics.

Introduction

According to the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines, severe asthma is defined as asthma requiring treatment based on Global Initiative for Asthma (GINA) steps 4–5 for the previous year or oral corticosteroids for ⩾50% of the previous year either to prevent the disease becoming uncontrolled or disease which remains uncontrolled despite this therapy [1]. Even though severe asthma only affects 5–10% of the total population with asthma [1], it represents a significant socioeconomic [2–6], psychological [7, 8] and treatment [9] burden, and is also be associated with risk of mortality [10, 11].

Over the past decades, new biological drugs have demonstrated a positive impact on the lives of many patients with severe asthma by reducing the frequency of exacerbations and dose of oral corticosteroids, and by improving lung function [12–15]. Recently, in addition to total IgE, blood eosinophil counts and fractional exhaled nitric oxide (F_{ENO}) have been suggested as a guide to initiate anti-IgE treatment in adolescents and adults [16]. Furthermore, blood eosinophil counts have been used to select patients for anti-interleukin (IL)-5 in adults [16], and F_{ENO}/blood eosinophil counts for dupilumab in adolescents and adults [17]. Several studies have described the characteristics of patients who started biologics [18, 19] and the characteristics of responders to treatment [20–23]. It has been shown that some patients reached a "super-response" [24] or "partial response" [25], whereas others experienced a "non-response" [24] or even deterioration [26] of clinical and patient-reported outcome measures (PROMs).

Although many studies have measured responses to different biologics, there are no universally accepted criteria for what constitutes response, and the absence of guidance on criteria is reported as a high-priority research gap in both children and adults [27, 28]. Evidence about responder definitions is critical for understanding the effectiveness of treatment for patients [29], clinicians and regulatory bodies, such as the European Medicines Agency [30] and the Food and Drug Administration [31]. Minimal clinically important difference (MCID) [32] and minimal important difference (MID) [33] are often used for assessing responses; these are defined as the smallest relevant within-person change or group differences between treatments, respectively. According to the Food and Drug Administration report, it is useful to report intra-subject responses based on an *a priori* responder definition [31]. In November 2016, an ERS Task Force reached a consensus on a traffic-light system to classify patients as non-responders, intermediate responders or super-responders [34]. The Task Force suggested that patients need to be on biological treatment for at least 4 months before an initial assessment of response can be determined [34]. However, this proposal has neither been validated nor further developed.

Given the unmet need to use consistent definitions of response for paediatric and adult patients, we aimed to 1) synthesise evidence about definitions of non-response and response to biological therapy used in patients with severe asthma, 2) assess the quality of the evidence for these definitions, and 3) evaluate the development, measurement properties and quality of outcome measures as supporting evidence for the included definitions. We chose to restrict our systematic review to studies where definitions were methodologically developed, defined and evaluated. Comprehensive assessment of response in clinical practice and trials using prespecified consensus criteria should provide useful guidance for clinical decision making, allow comparison across studies, eliminate unnecessary treatment in patients with inadequate response and ensure that the high cost associated with biological therapies [35] is justified [36].

Methods

This was a systematic review conducted by the 3TR (Taxonomy, Treatment, Targets and Remission) [37] Respiratory Work Package members and external collaborators including academic clinicians, regulatory, patient and pharmaceutical representatives from across Europe. The study is registered at PROSPERO with identifier number CRD42021211249. Our aim was to look at response in severe asthma, but in anticipation that the evidence base would be limited, we initially included studies of all severities of asthma. However, given that there is evidence for definitions of response to biological therapy for severe asthma, the protocol was revised to restrict the systematic review to studies of severe asthma. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist has been used to structure this

article (supplementary appendix 1) [38]. The methods are briefly described here. Details are available in the supplementary material.

Search strategy

Four databases were searched (Embase (OVID), MEDLINE (OVID), CINAHL (EBSCOhost, Cumulative Index to Nursing and Allied Health Literature) and ISI Web of Science (Thomson Web of Knowledge)) using a search strategy developed on Embase (OVID) and then adapted for other databases (supplementary appendix 2). In summary, the search strategy was designed to identify papers focused on "asthma" AND "a biological therapy" AND "response/treatment outcome/minimal important difference". Databases were searched from inception to 15 March 2021. Additional references were searched through the references cited by the identified studies, systematic reviews, reviews, guidelines or highlighted by experts in the field.

Inclusion criteria

Studies were eligible for inclusion if they met the following criteria. 1) Population: children/adolescents (6 –17 years) and/or adults (⩾18 years) with a diagnosis of severe asthma. 2) Intervention: any biological therapy which was investigated and/or currently used for severe asthma. 3) Comparator: any comparator, including placebo or no comparator. 4) Outcomes: any definitions of non-response and response to biological therapy for severe asthma which were methodologically developed, defined and evaluated. Sole or a composite of clinical, patient-reported, biological and/or imaging outcome measures were eligible for inclusion. Additional evidence about these outcome measures including development (undertaken in studies of any severity of asthma) and validation (conducted in studies with biologics for severe asthma) was included. 5) Study types: randomised controlled trials, cross-sectional studies, controlled before-and-after studies, non-randomised controlled studies, case–control studies in humans, cohort studies and consecutive case series (with a minimum of 10 participants) published as full-text articles and letters published in English were eligible for inclusion. Additional evidence about development and validation of outcome measures was considered from qualitative and validation studies.

Exclusion criteria

The following were excluded from the analysis: systematic reviews and meta-analyses, narrative reviews, discussion papers, editorials, commentaries, case reports, animal studies, conference abstracts, studies not available in full form, studies published in a language other than English, unpublished material and non-asthma studies (*e.g.* viral bronchiolitis or viral-associated wheeze). Studies were also excluded if they only used outcome measures and definitions of response to assess treatment effectiveness or efficacy.

Study selection

All references were pooled and de-duplicated in Endnote version X9 (Thomson Reuters, Philadelphia, PA, USA) and subsequently uploaded to Rayyan (https://rayyan.qcri.org), where any remaining duplicates were removed. Titles, abstracts and full texts were screened independently by two reviewers (E.K. and A.R.) according to the predefined selection criteria and categorised as included, excluded or unsure. Any disagreements were resolved through discussion with a third reviewer (G.R.).

Data extraction, risk of bias assessment, quality and synthesis of the results

Data extraction was based on the COnsensus-based Standards for the selection of Measurement INstruments (COSMIN) guideline for outcome measures [39]. Definitions of the measurement properties provided by COSMIN are provided in supplementary table S1 and criteria for good measurement properties (GMPs) are provided in supplementary table S2.

Risk of bias of individual studies was assessed using the COSMIN checklist for PROMs [40, 41] and composite outcome measures (COSMIN risk of bias for non-patient-reported outcomes) [42]. Risk of bias for each measurement property in the validation studies was rated as very good, adequate, doubtful or inadequate. The certainty of evidence was assessed using the modified GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach [39, 41, 43]. Data extraction, risk of bias assessment and modified GRADE were completed independently by two reviewers (E.K. and A.R.). Any discrepancies were resolved by discussion or by a third reviewer (G.R.). A descriptive synopsis with summary data tables was produced and results were summarised using narrative synthesis. Detailed methods are provided in supplementary appendix 3. The results were reviewed and discussed within the Core Outcome Measures for Severe Asthma (COMSA) initiative [44] that included a multidisciplinary, European group of academic clinicians, regulatory, patient and pharmaceutical representatives. The group aimed to select the core outcome measure sets for paediatric and adult severe asthma.

Results

Description of studies

Our search strategy identified a total of 11 588 papers; 11 553 articles were excluded after title and abstract screening. The full text of 35 papers was assessed for eligibility, including 20 articles identified through review of citations. 13 papers were included in the systematic review, of which three were about development of the outcome measures [45–47], five were validation papers [48–52], and five reported development and validation data in the same paper [53–57] (figure 1).

Development and quality of definitions of non-response and response

The approach to development of definitions and their characteristics are shown in tables 1 and 2. Definitions were developed for three composite asthma outcome measures [52–54], three asthma symptom outcome measures [50, 51], one asthma control outcome measure [56] and one quality of life (QoL) measure [49]. The following methods of development were used: consensus [54, 56], anchor-based [49–52] and distribution-based [53] methods. 10 definitions measured response based on MCID [49, 50, 52] or MID [51, 53] and seven [51, 56] based on responder/non-responder levels. Omalizumab [49, 52, 53, 56], brodalumab [51], benralizumab [49, 54], reslizumab [49, 54] and mepolizumab [49, 50, 54] were predominantly used in these studies. Response was evaluated at different time-points, including as early as 4 weeks [49] and up to 60 weeks [52]. Most definitions were developed for adults [49–51, 53, 54], while three were for adolescents [50, 52, 53] and one was for children [52] with severe asthma. Quality of evidence for definitions of response was rated as "high" for all except "moderate" for the Asthma Severity Scoring System (ASSESS) [53] due to a lower number of patients taking biologics.

Development and content validity of the outcome measures

An overview of the developmental process and its quality are shown in table 2 and supplementary table S3. The developmental process was predominantly rated as "sufficient", while quality of evidence was mainly "very low" to "low", but "moderate" for the Severe Asthma Questionnaire (SAQ) [46, 55]. Three composite outcome measures were developed by physicians, including FEOS (forced expiratory volume in 1 s (FEV_1), exacerbations, oral corticosteroids, symptoms score) [54] for adults and ASSESS [53] which was adapted from the Composite Asthma Symptom Index (CASI) [57] for adolescents/adults and children with asthma, respectively. The Global Evaluation of Treatment Effectiveness (GETE) [56] scale was also developed by physicians. Only four outcomes were developed with patient input, including the SAQ [46, 55], Asthma Symptom Diary (ASD) [45], Asthma Symptom Utility Index (ASUI) [50] and Asthma Symptom Index (ASI) [47], which was adapted from the ASUI by excluding questions about medication side-effects. A summary of key instrument characteristics and feasibility is provided table 3 and supplementary table S4.

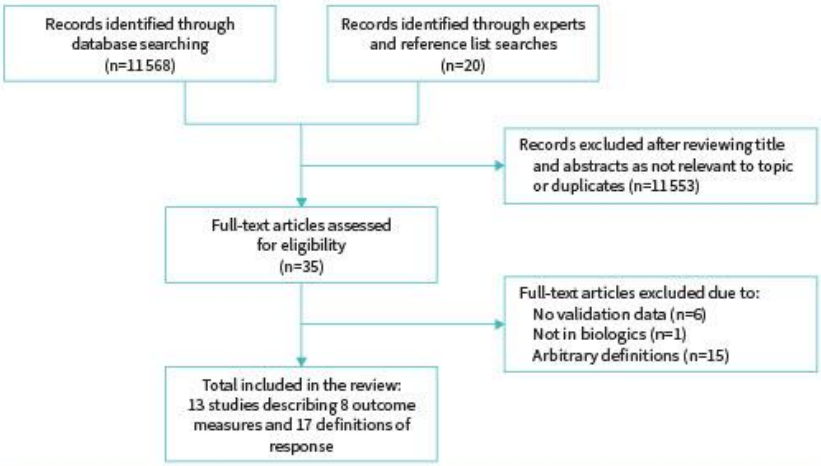

FIGURE 1 PRISMA diagram demonstrating study selection.

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TABLE 1 Characteristics of included studies

Study, year [ref.]	Scale	Study design	Patients (n)	Age (years)	Patient characteristics	Asthma severity (severe %)	Definition of asthma	Biological therapy
Composite outcome measures								
Fitzpatrick, 2020 [53]	ASSESS	Post-hoc analysis of 2 RCTs	562	44±0.7	Female 64.1%; FEV_1 74.2±0.9% predicted	Mild to severe (58.4%)	Modified ERS/ATS	Omalizumab (n=43)
Krouse, 2017 [52]#	CASI	Post-hoc analysis of RCT	419	10.8 (IQR 8–14)	Female 42.2%; FEV_1 92.0% predicted	Mild to severe (54.0%)	NAEPP	Omalizumab (n=208)
Pérez de Llano, 2021 [54]	FEOS	NR	14	NR	NR	Severe (100.0%)	GINA step 5, ERS/ATS	Reslizumab (n=6), mepolizumab (n=5), benralizumab (n=3)
Asthma symptom outcome measures								
Shen, 2021 [50]	ASUI	Post-hoc analysis of RCT	497	51.0±13.6	Female 59.2%; FEV_1 58.8±15.7% predicted	Severe eosinophilic (100.0%)	ERS/ATS	Mepolizumab (n=269)
Shen, 2021 [50]	ASI	Post-hoc analysis of RCT	497	51.0±13.6	Female 59.2%; FEV_1 58.8±15.7% predicted	Severe eosinophilic (100.0%)	ERS/ATS	Mepolizumab (n=269)
Globe, 2019 [51]	ASD	Post-hoc analysis of RCT	417	47.3±13.6	Female 59.0%	Moderate-severe	Doctor-diagnosed	Brodalumab (n=283)
Asthma control outcome measures								
Lloyd, 2007 [56]	GETE	Post-hoc analysis of 3 RCTs	1380	12–76¶	NR	Moderate-severe	GINA, ATS, NHLBI	Omalizumab+
Asthma quality of life outcome measures								
Masou, 2021 [49]	SAQ	Longitudinal cohort	110	49.0	Female 69.0%; FEV_1 67.0% predicted	Severe (100.0%)	ERS/ATS	Omalizumab (n=16), mepolizumab (n=26), benralizumab (n=62), reslizumab (n=2)

ACT: Asthma Control Test; ATS: American Thoracic Society; ASSESS: Asthma Severity Scoring System; ASUI: Asthma Symptom Utility Index; ASI: Asthma Symptom Index; ASD: Asthma Symptom Diary; CASI: Composite Asthma Severity Index; ERS: European Respiratory Society; FEOS: FEV_1, exacerbations, oral corticosteroids, symptoms score; FEV_1: forced expiratory volume in 1 s; GETE: Global Evaluation of Treatment Effectiveness; GINA: Global Initiative for Asthma; IQR: interquartile range; NHLBI: National Heart, Lung, and Blood Institute; NAEPP: National Asthma Education and Prevention Program; NR: not reported; RCT: randomised controlled trial; SAQ: Severe Asthma Questionnaire. #: definition was developed in mild to severe asthma and then evaluated in patients taking biological therapy; ¶: inclusion criteria are reported as the mean age of the participants is unclear; +: n=1380 patients from the randomised, placebo-controlled, double-blind studies were included in the analysis.

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TABLE 2 Definitions of non-response and response to biological therapy for severe asthma and their quality of evidence

Study, year [ref.]	Scale	Patient input in scale development	Time-point from baseline	Method of development of definition of response	Definition of response	Range of scores	GRADE
Composite outcome measures							
Fitzpatrick, 2020 [53]	ASSESS	No	12 months	Distribution-based method	MID 2 points	0–20 points (higher=worse)	⊕⊕⊕○A
Krouse, 2017 [52]#	CASI	No	60 weeks	Anchor-based method	MCID 1 point	0–18 points (higher=worse)	⊕⊕⊕⊕
Pérez de Llano, 2021 [54]	FEOS	No	NR	Delphi exercise, conjoint analysis	Response defined according to different thresholds for each outcome measure with respect to baseline; response ranges from 0 (worsening) to 100 (best)	0–100 points (higher=better)	⊕⊕⊕⊕
Asthma symptom outcome measures							
Shen, 2021 [50]	ASUI	Yes	12 weeks	Anchor-based method	MCID 0.07 to 0.11	0–1 points (higher=better)	⊕⊕⊕⊕
Shen, 2021 [50]	ASI	Yes	12 weeks	Anchor-based method	MCID −0.42 to −0.26	0–3 points (higher=worse)	⊕⊕⊕⊕
Globe, 2019 [51]	ASD¶	Yes	12, 24 weeks	MID (change −0.5 to −1.0 ACQ); responder (change ⩽ −1.0 ACQ)	Reported for 12 and 24 weeks: Mean 7-day score: MID −0.35 and −0.35; responder −0.54 and −0.68 7-day symptomatic days: MID −1.75 and −1.98; responder −2.34 and −3.22 Minimal symptomatic days-1: MID 1.97 and 2.16; responder 2.43 and 3.23 Minimal symptomatic days-2: MID 1.02 and 1.36; responder 2.31 and 2.56	0–4 points (higher=worse)	⊕⊕⊕⊕
Asthma control outcome measure							
Lloyd, 2007 [56]	GETE	No	28 weeks	Physician consensus	Responder (complete control; marked improvement of asthma); non-responder (discernible, but limited improvement in asthma, no appreciable change in asthma; worsening of asthma)	0–5 points (higher=better)	⊕⊕⊕⊕
Asthma quality of life outcome measure							
Masou, 2021 [49]	SAQ	Yes	4, 8, 12 weeks	Anchor-based method	MCID (SAQ) 0.5 points; MCID (SAQ-global) 11 points	SAQ: 1–7 points; SAQ-global: 0–100 points (higher=better)	⊕⊕⊕⊕

ACQ: Asthma Control Questionnaire; ASSESS: Asthma Severity Scoring System; ASUI: Asthma Symptom Utility Index; ASI: Asthma Symptom Index; ASD: Asthma Symptom Diary; CASI: Composite Asthma Severity Index; FEOS: forced expiratory volume in 1 s, exacerbations, oral corticosteroids, symptoms score; GETE: Global Evaluation of Treatment Effectiveness; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; MCID: Minimal Clinically Important Difference; MID: Minimal Important Difference; NR: not reported; SAQ: Severe Asthma Questionnaire. #: definition was developed in mild to severe using anchor-based method and then evaluated in biologicals (MID was changed to MCID by the review team); ¶: symptomatic days (defined as mean of the 10 ASD daily symptom items ⩾1, otherwise non-symptomatic day), minimal symptom days-1 (defined as mean of the 10 ASD daily symptom items ⩽1 and no single symptom item score>1, otherwise non-minimal symptom day-1) and minimal symptom days-2 (defined as no single ASD daily symptom item). Certainty of evidence was assessed using the GRADE approach [39, 41, 43]. The reason for downgrading was: A: indirectness.

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TABLE 3 Summary of the characteristics of the outcome measures

	Recall period	Outcome measure content								
		ACT	Asthma control	Albuterol day/night	Asthma symptoms	Exacerbations	Asthma medications	mOCS	FEV_1	Quality of life
ASSESS [53]	Current (FEV_1, asthma medications); 4 weeks (ACT); 6 months (exacerbations)	X				X	X		X	
CASI [57]	Current (FEV_1, asthma medications); 2 weeks (symptoms, albuterol use); 2 months (exacerbations)			X	X	X	X		X	
FEOS [54]	Baseline to current (FEV_1 and mOCS); 4 weeks (ACT); 12 months (severe exacerbations)	X				X		X	X	
ASUI [50]	2 weeks				X					
ASI [50]	2 weeks				X					
ASD [45]	Current (morning and evening)				X					
GETE [56]	Baseline to current		X							
SAQ [46]	2 weeks									X

ACT: Asthma Control Test; ASSESS: Asthma Severity Scoring System; ASUI: Asthma Symptom Utility Index; ASI: Asthma Symptom Index; ASD: Asthma Symptom Diary; CASI: Composite Asthma Severity Index; GETE: Global Evaluation of Treatment Effectiveness; FEOS: FEV_1, exacerbations, oral corticosteroids, symptoms score; FEV_1: forced expiratory volume in 1 s; mOCS: maintenance oral corticosteroids; SAQ: Severe Asthma Questionnaire. The ASUI and ASI measure frequency and severity of asthma symptoms (cough, wheeze, shortness of breath and night-time awakening), while the ASD measures morning and evening symptoms separately (wheeze, shortness of breath, cough, chest tightness, night-time awakening or impairment of daily activities). The GETE measures effectiveness of biological treatment based on physician and patient view separately.

Risk of bias and quality of evidence for validation studies of outcome measures

Validation data including risk of bias are shown in supplementary tables S5–S7 and methodological quality of the outcome measures rated against criteria for GMPs is presented in table 4. Overall, almost all outcome measures had "inadequate" risk of bias due to lack of involvement of patients in the development, many measurement properties not being reported and none of the studies reporting cross-cultural validity including measurement invariance.

The GETE [56] scale has patient and physician versions which demonstrated high quality of evidence for construct validity, although there was a positive skew towards "complete control of asthma" and "marked improvement of asthma" possibly due to the ceiling effect. The CASI [57] showed insufficient responsiveness but "high" quality of evidence. Sufficient measurement properties were rated for ASSESS, including test–retest reliability, construct validity and responsiveness to change, while the quality was mostly "very low". The ASUI [50] and ASI [50] performed similarly and showed sufficient rating against GMP criteria and "low" to "high" quality. The SAQ [48, 49, 55] again showed sufficient properties and "very low" to "moderate" quality of evidence. Only responsiveness to change was evaluated for the ASD [51] as assessment of other measurement properties was not performed in patients taking biologics for severe asthma. The FEOS [54] scale only contains data about inter-rater agreement which was not possible to assess based on the COSMIN methodology.

Discussion

This study aimed to review the literature on definitions of response and non-response to biological therapy for severe asthma. To the best of our knowledge, the current systematic review is the first to synthesise methodologically developed, defined and evidenced definitions. We identified eight outcome measures: three composite outcome measures, three measuring asthma symptoms, one measuring asthma control and one measuring QoL. Studies utilised a variety of definitions of response criteria, mostly using MCIDs or MIDs where available and measured at different time-points for different biologics. Only GETE [56] defined a non-response, while FEOS [54] is a scale ranging from 0 to 100 (best), with no established cut-off for non-responders.

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TABLE 4 Evaluation of outcome measures against good measurement properties (GMPs) and their quality of evidence

	ASSESS [53]		CASI [57][a]		FEOS [54]		ASUI [47, 50]		ASI [50]		ASD [45, 51]		GETE [56][¶]		SAQ [46, 48, 49, 55][+]	
	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE
Relevance	+	⊕○○○^{A,B,C}	+	⊕○○○^{A,C}	+	⊕○○○^{A,C}	±	⊕⊕○○^{A,C}	±	⊕⊕○○^{A,C}	±	⊕⊕○○^{A,C}	+	⊕○○○^{A,B,C}	+	⊕⊕⊕○^{A}
Comprehensiveness	+	⊕○○○^{A,B,C}	–	⊕○○○^{A,C}	±	⊕○○○^{A,B,C}	±	⊕○○○^{A,B,C}	-	⊕○○○^{A,B,C}	+	⊕⊕○○^{A,C}	–	⊕○○○^{A,B,C}	+	⊕⊕⊕○^{A}
Comprehensibility	+	⊕○○○^{A,B,C}	±	⊕○○○^{A,C}	+	⊕○○○^{A,C}	+	⊕○○○^{A,B,C}	+	⊕○○○^{A,B,C}	+	⊕⊕○○^{A,C}	+	⊕○○○^{A,B,C}	+	⊕⊕⊕○^{A}
Reliability	+	⊕○○○^{A,C}	?		?		+	⊕⊕⊕○^{A}	+	⊕⊕⊕○^{A}	?		?		+[f]	⊕⊕○○^{A,C}
Construct validity[§]	+	⊕⊕○○^{A,C}	?		?		+	⊕⊕○○^{A}	+	⊕⊕○○^{A}	?		+	⊕⊕⊕⊕	+[f]	⊕⊕○○^{A,C}
Responsiveness	+	⊕○○○^{A,C}	–	⊕⊕⊕⊕	?		+	⊕⊕○○^{A}	+	⊕⊕○○^{A}	+	⊕⊕○○^{A}	?		+[f]	⊕⊕○○^{A,C}

GMPs for each measurement property were rated based on the COSMIN criteria [39, 41] as either sufficient (+), insufficient (–), indeterminate (?) or inconsistent (±, for development criteria only). Empty cells or indeterminate ratings indicate that the measurement property was not investigated or there is insufficient information. Structural validity, internal consistency, measurement error and cross-cultural validity are not shown in the table for all outcome measures due to the same reasons. For construct validity and responsiveness, the review team formulated *a priori* hypotheses about the expected relationships between an outcome measure and comparator instruments. Overall, ⩾75% of the pooled results for the measurement property were expected to meet the criteria in order to be classified as a sufficient rating [39]. ASUI: Asthma Symptom Utility Index; ASI: Asthma Symptom Index; ASSESS: Asthma Severity Scoring System; ASD: asthma symptom diary; CASI: Composite Asthma Severity Index; FEOS: forced expiratory volume in 1 s, exacerbations, oral corticosteroids, symptoms score; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; GETE: Global Evaluation of Treatment Effectiveness; SAQ: Severe Asthma Questionnaire. [#]: only external validation data were used for analysis as it was performed in a study with biologics; [¶]: physician and patient version of the GETE were graded similarly (assessment of the development was based on reviewer rating only); [+]: the SAQ is based on a formative model; therefore, there was no need to assess structural validity and internal consistency. [§]: as there is no gold standard in asthma, data about criterion validity were combined with construct validity; [f]: ratings apply to SAQ subscales (My Life, My Mind, My Body) and SAQ-global. Certainty of evidence was assessed using the modified GRADE approach as "high", "moderate", "low" or "very low" [39, 41, 43]. The reasons for downgrading were: A: risk of bias; B: inconsistency; C: indirectness.

One of the aims of the review was to assess the development and measurement properties of the identified outcome measures. Results were limited by "very low" to "low" quality of evidence for the development process, except for the SAQ [46, 55], and incomplete reporting of measurement properties for all outcome measures. Based on the COSMIN guideline, none of the outcome measures met all the quality standards. Only four outcome measures were developed with patient input, even though this is considered as a vital step in ensuring that the instrument is meaningful for patients. Responsiveness to change was rated as "low" to "very low", while definitions of response had "high" quality except for ASSESS [53].

Evaluation of therapeutic response in asthma has received increased attention with the introduction of biological treatments to improve disease treatment and precision management [58]. More than 70% of patients achieved good or excellent response to omalizumab based on GETE [59]; however, this relies on a single global measure to reflect the heterogeneous response to biological treatment. Thus, GETE does not discriminate the different effects of a treatment on different response areas, such as QoL, exacerbations, maintenance corticosteroid use and lung function. Two asthma symptoms questionnaires (ASUI and ASI [50]) were designed to assess cost-effectiveness of treatment, while the ASD [51] is a symptom diary and might impose too much burden on participants of biological therapy trials. The SAQ [55], which was developed with patient input, showed the best quality of evidence and was selected in the COMSA [44, 60].

Several composite outcome measures were identified. Neither the CASI [57] nor ASSESS [53] include a QoL domain, and the CASI [57] does not assess maintenance oral corticosteroid use, even though reduction in oral corticosteroid use and improvement of QoL have been shown to be the best indicators of response to treatment for patients with severe asthma [61]. The 2-point MID for ASSESS showed good specificity but poor sensitivity and the authors suggested that it should be interpreted with caution until more data are available [53]. The FEOS tool to quantify response [54] was developed for adults with severe asthma using novel methodology, but patients were not involved in the selection of outcome measures and it may not also represent the perspectives of international stakeholders. Unlike the COMSA initiative [44], the validity of the included outcome measures for severe asthma was not assessed and exclusion of aspects such as QoL may not represent a patient-centred approach.

This systematic review did not identify any studies which validated definitions of response to biological therapy using clinical outcome measures in patients with severe asthma. Some data are available from the consensus statements, *e.g.* the MID for FEV_1 is 0.20 L [13] or 10% improvement [62] and for F_{ENO} a reduction of $\geqslant$20% for values over 50 ppb (or $\geqslant$10 ppb for values lower than 50 ppb) should be used to indicate response to anti-inflammatory therapy [63]. While a published composite definition of exacerbation has been developed and validated in patients with severe asthma taking benralizumab, no MCID data are available yet [64].

Most outcome measures identified in the systematic review utilised MCIDs or MIDs to assess response, but we do not regard these definitions as interchangeable, *e.g.* in one paper the term MID was used when it would seem to be more appropriate to use MCID [52]. An improvement that patients might recognise as equivalent to the MCID with an inhaled asthma therapy may potentially be rated as less than the MCID in the context of high-cost biologics administered by injection [35, 36]. Also, to be regarded as cost-effective a biological therapy will demand a greater magnitude of response than a less expensive asthma therapy. A further critical variable may be the duration of response, given the case reports of secondary loss of response [65], *i.e.* the loss of response during the treatment over time despite an initial primary response [66, 67].

The concept of "super-responders" to biological treatment has emerged recently [24, 68]. In order to standardise the definition, a modified Delphi exercise among healthcare professionals has been conducted but there is a need to understand patient perspectives [69]. The rate of super-responders in patients prescribed anti-IL-5 depending on criteria ranges from 14% to 28% [24, 68, 70], forming a small but important group. Super-response should be the ultimate goal of treatment. However, patients who fail to achieve such a level of improvement may still benefit from biological therapies. Nevertheless, consideration should be given in such cases as to whether a different biologic may be more beneficial. Evaluation of a complete response, as in haematological disorders [71, 72], should be explored further in severe asthma even though only a very small percentage of patients experience remission [73].

Unfortunately, some patients with severe asthma do not respond to biological therapy and may even deteriorate. Differences in treatment response may be multifactorial, reflecting medicinal and/or subject variables including mechanisms of action, target, dose and interval of the biological drug or heterogeneity of asthma phenotypes [74]. For example, non-response might reflect differences in the pharmacokinetics of

biological drugs; indeed, monitoring plasma monoclonal antibody levels appears useful in various chronic diseases [75–77].

Overall, assessing the non-response and response after several months of treatment with biologics facilitates cost control by reducing the duration of ineffective therapy, and should enable better quality of care and patient experience by prescribing alternative treatments including switching to another biological if appropriate [78]. The latter is especially important given the rapidly increasing number of therapeutic options for patients with severe asthma [1, 16].

Strengths and limitations

This systematic review was conducted by a diverse group of academic clinicians, patient representatives, and regulatory and pharmaceutical representatives. This was a strength because it meant that definitions were considered on clinical and patient-centred grounds. A comprehensive search was conducted in four databases and provides a summary of the robust research. Rigorous methods were used including risk of bias assessment and GMPs based on COSMIN followed by the modified GRADE approach to rate the certainty of the evidence. Using transparent and validated COSMIN [39–41] methodology helped to standardise the quality assessment of outcome measures and reduce bias. Many studies were excluded as they used arbitrary definitions of response; only methodologically developed definitions and validated outcome measures were considered for inclusion in the systematic review. Lastly, all studies used data from a large number of paediatric and adult patients with severe asthma who were treated with a variety of biological therapies such as omalizumab, brodalumab, benralizumab, reslizumab and mepolizumab.

Nevertheless, we recognise several limitations. First, only studies published in English were included; however, we screened studies included in the guidelines, previous systematic reviews, references of identified articles and reviews, which made it highly unlikely that relevant studies were missed. Second, the search was conducted in 2021 as part of the development of the COMSA which was published in 2023 [44]. Third, we only searched the literature related to biological therapies and did not look at the evidence from response to non-biological asthma therapies. Biologics have different mechanisms of action, administration approaches, costs and potential adverse effects. Therefore, response criteria could differ with different patient views on what counts as a beneficial response given these considerations. However, it may be possible to also learn from the response to other therapies such as to oral and inhaled corticosteroids in severe asthma. Fourth, definitions of therapeutic response were assessed at different time-points, which might make it difficult to come to definitive conclusions about non-responders and responders. Moreover, COSMIN suggest using the lowest score counts method to assess measurement properties, meaning that having higher quality scores on some items of the checklist was not considered and only the "worst score" was reported. Lastly, it was not possible to run a meta-analysis due to low number of studies per outcome measure and only narrative synthesis was undertaken.

Policy implications and next steps

This systematic review aimed to inform clinicians, regulators and policy makers about the gaps and highlight heterogeneity of the definitions used. Even though the Asthma Control Questionnaire/Test and Asthma Quality of Life Questionnaire are widely used in phase 3 trials of asthma biologics and in clinical practice, definitions of response including MCID or MID have never been specifically assessed in biologics. Further research should aim to explore the identified definitions as primary and secondary outcomes in clinical trials including phase 2 and 3 efficacy studies and assess the MCID/MID of well-validated questionnaires in biological trials. There is also a need to methodologically develop patient-centred definitions of non-response and response to biological therapy for severe asthma for individual PROMs and clinical as well as a composite outcome measures. For example, based on COSMIN methodology for assessing the content validity of PROMs [41], patients should be asked about their relevance, comprehensiveness and comprehensibility. Engagement of patients is a crucial aspect of the development of outcome measures to meet their needs and preferences as well as to inform health decisions [79, 80].

Given the aforementioned, we are planning to develop definitions of non-response and response to biological therapies for paediatric and adult severe asthma trials and clinical practice based on the COMSA selected among key stakeholder groups, including patients with severe asthma [44]. We aim to standardise the definitions, which will allow better tailoring of individual treatment and be used in future clinical trials for documenting therapeutic response. Furthermore, looking at multiple dimensions of asthma such as exacerbations, QoL, asthma control and lung function in one single patient-centred composite would help to determine the correct sample size for future clinical trials, assist regulators in determining whether a new biological therapy is effective and identify predictors of treatment response. Use of such definitions will

also help in better understanding the applicability of novel biomarkers such as volatile organic compounds [81], peripheral blood gene expression [82, 83] and serum periostin [84] in the prediction and monitoring of response, which have been shown to be promising in biological treatment for severe asthma.

Conclusions

This systematic review is the first to evaluate the quality of evidence for definitions of response to biological therapy for severe asthma and measurement properties of associated outcome measures. There are several high-quality definitions available for use that are mostly based on MIDs or MCIDs, which might not be sufficient to justify continuation of biological therapy on cost-effectiveness criteria. Even though composite outcome measures are available and able to capture the multidimensional nature of severe asthma, none were developed with patient input and all lack a QoL component. Quality of evidence for the development and validation of the outcome measures was rated predominantly "low" and "very low", and none met all the methodological quality standards, highlighting an urgent unmet need. Therefore, the forthcoming 3TR project will aim to develop the definitions of non-response and response based on COMSA [44] with involvement of patient representatives and other key stakeholders. Future research will be needed to pilot these definitions in biological trials, and to address practical implications for policy makers, research and clinical practice. Knowing how to evaluate response to biologics using universally acceptable criteria would help in assessing the effectiveness of novel therapies, and improve clinical decision making and the care of patients with severe asthma.

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Author contributions: E. Khaleva developed a protocol and a search strategy, and G. Roberts and A. Rattu reviewed this. E. Khaleva and A. Rattu performed abstract screening, data extraction and COSMIN evaluation. E. Khaleva synthesised the evidence and wrote the first draft of the manuscript. All authors critically reviewed the manuscript and approved the final version prior to submission.

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Supplementary materials

Definitions of non-response and response to biological therapy for severe asthma: a systematic review.

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Appendix 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods- inclusion criteria; exclusion criteria
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods-Search strategy
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary materials
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods-Study selection
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods- Data extraction, risk of bias assessment, quality, and synthesis of the results
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Appendix 3.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Appendix 3.
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Data extraction, risk of bias assessment, quality, and synthesis of the results
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	NA
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Appendix 3.
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods- Data extraction, risk of bias assessment, quality, and synthesis of the results
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1; 2; S3; S6;
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table S7
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	NA
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results- Development and quality of definitions of non-response and response; Development and content validity of the outcome measures; Risk of bias and quality of evidence for validation studies of outcome measures
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results-Risk of bias and

Section and Topic	Item #	Checklist item	Location where item is reported
evidence			quality of evidence for validation studies of outcome measures
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion: Strengths and limitations
	23c	Discuss any limitations of the review processes used.	Discussion: Strengths and limitations
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion: Policy implications and next steps
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Methods
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding
Competing interests	26	Declare any competing interests of review authors.	Conflict of interests
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplementary materials

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Appendix 2. Search strategies

I. Search strategy in EMBASE (OVID)

1. asthma/ or allergic asthma/ or aspirin exacerbated respiratory disease/ or asthmatic state/ or exercise induced asthma/ or experimental asthma/ or extrinsic asthma/ or intrinsic asthma/ or mild intermittent asthma/ or mild persistent asthma/ or moderate persistent asthma/ or nocturnal asthma/ or occupational asthma/ or severe persistent asthma/

2. asthma*.ti,ab.

3. 1 or 2

4. omalizumab.mp. or exp omalizumab/

5. mepolizumab.mp. or exp mepolizumab/

6. reslizumab.mp. or reslizumab/

7. benralizumab.mp. or exp benralizumab/

8. dupilumab.mp. or exp dupilumab/

9. tralokinumab.mp. or exp tralokinumab/

10. lebrikizumab.mp. or exp lebrikizumab/

11. tezepelumab.mp. or exp tezepelumab/

12. brodalumab.mp. or exp brodalumab/

13. ligelizumab.mp. or exp ligelizumab/

14. Pitrakinra.mp. or pitrakinra/

15. exp biological product/ or exp biological therapy/ or biologic*.mp.

16. (biologic* adj1 (treatment* or therap* or medicine* or drug* or agent* or product*)).mp.

17. monoclonal antibod*.mp. or exp monoclonal antibody/

18. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19. drug response/ or exp treatment response/ or partial drug response/

20. (responsive* or response or respond* or nonrespon*).mp.

21. treatment outcome/ or outcome assessment/

22. minimal clinically important difference/ or meaningful change.mp.

23. (Minimal* adj1 (clinical* or important or real or significant) adj1 (change or difference)).mp.

24. (Minimal* adj1 clinical* adj1 (important or significant) adj1 (change or difference)).mp.

25. (MCID or MID or MIC).mp.

26. 19 or 20 or 21 or 22 or 23 or 24 or 25

27. editorial/ or review/ or case report/ or case report*.mp.

28. editorial*.mp.

29. conference abstract*.mp.

30. conference paper*.mp. or conference paper/ or conference abstract/

31. ((systematic or narrative) adj2 review*).mp. or "systematic review"/

32. ((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire*)) or ("focus group*" or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).ti,ab. or survey*.ti.

33. interview/ or information processing/ or verbal communication/ or qualitative research/ or exp short survey/ or exp health care survey/ or exp health survey/

34. 27 or 28 or 29 or 30 or 31 or 32 or 33

35. 3 and 18 and 26

36. 35 not 34

37. 36 not ((exp animal/ or nonhuman/) not exp human/)

38. limit 37 to english language

II. Search strategy in MEDLINE (OVID)

1. exp Asthma, Aspirin-Induced/ or exp Asthma, Exercise-Induced/ or exp Asthma/ or exp Asthma, Occupational/ or asthma*.ti,ab.

2. omalizumab.mp. or Omalizumab/

3. mepolizumab.mp.

4. reslizumab.mp.

5. benralizumab.mp.

6. dupilumab.mp.

7. tralokinumab.mp.

8. lebrikizumab.mp.

9. tezepelumab.mp.

10. brodalumab.mp.

11. ligelizumab.mp.

12. Pitrakinra.mp.

13. biological product/ or biological therapy/ or biologic*.mp.

14. (biologic* adj1 (treatment* or therap* or medicine* or drug* or agent* or product*)).mp.

15. monoclonal antibod*.mp. or antibodies, monoclonal/ or antibodies, monoclonal, humanized/

16. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17. (responsive* or response or respond* or nonrespon*).mp.

18. treatment outcome/ or Outcome Assessment, Health Care/

19. Minimal Clinically Important Difference/ or meaningful change.mp.

20. (Minimal* adj1 (clinical* or important or real or significant) adj1 (change or difference)).mp.

21. (Minimal* adj1 clinical* adj1 (important or significant) adj1 (change or difference)).mp.

22. (MCID or MID or MIC).mp.

23. 17 or 18 or 19 or 20 or 21 or 22

24. editorial/ or review/ or case report/ or case report*.mp.

25. (editorial* or conference abstract* or conference paper*).mp.

26. ((systematic or narrative) adj2 review*).mp. or "systematic review"/

27. ((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire*)) or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).ti,ab. or survey*.ti.

28. interviews as topic/ or focus groups/ or narration/ or qualitative research/ or health care surveys/ or health surveys/

29. 24 or 25 or 26 or 27 or 28

30. 1 and 16 and 23

31. 30 not 29

32. 31 not (Animals/ not (Animals/ and Humans/))

33. limit 32 to english language

III. Search strategy in CINAHL (EBSCOhost)

1. (MH "Asthma+") OR (MH "Asthma, Occupational") OR (MH "Asthma, Exercise-Induced") OR TI asthma* OR AB asthma*

2. "omalizumab" OR "mepolizumab" OR "reslizumab" OR "benralizumab" OR "dupilumab" OR "tralokinumab" OR "lebrikizumab" OR "tezepelumab" OR "brodalumab" OR "ligelizumab" OR "Pitrakinra" (MH "Biological Therapy") OR (MH "Antibodies, Monoclonal+") OR ((biologic*) N1 (treatment* OR therap* OR medicine* OR drug* OR agent* OR product*)) OR "biologic*" OR "monoclonal antibod*"

3. "responsive*" OR "response" OR "respond*" OR "nonrespon*" OR (MH "Treatment Outcomes") OR (MH "Outcome Assessment")

4. "MCID" OR "MID" OR "MIC" OR "meaningful change" OR (Minimal* N1 (clinical* OR important OR real OR significant) N1 (change OR difference)) OR (Minimal* N1 clinical* N1 (important OR significant) N1 (change OR difference))

5. TI (("semi-structured" OR semistructured OR unstructured OR informal OR "in-depth" OR indepth OR "face-to-face" OR structured OR guide) N3 (interview* OR discussion* OR questionnaire*)) OR TI ("focus group*" OR qualitative OR ethnograph* OR fieldwork OR "field work" OR "key informant"))

6. AB (("semi-structured" OR semistructured OR unstructured OR informal OR "in-depth" OR indepth OR "face-to-face" OR structured OR guide) N3 (interview* OR discussion* OR questionnaire*)) OR AB ("focus group*" OR qualitative OR ethnograph* OR fieldwork OR "field work" OR "key informant")

7. (MH "Qualitative Studies") OR (MH "Focus Groups") OR (MH "Narratives") OR (MH "Interviews") OR (MH "Surveys") OR TI Survey*

8. (MH "Literature Review") OR (MH "Scoping Review") OR PT "Systematic Review" OR PT review OR PT editorial OR PT proceedings

9. S3 OR S4

10. S5 OR S6 OR S7 OR S8

11. S1 AND S2 AND S9

12. S11 NOT S10

13. (MH "Animals+") NOT (MH "Human")

14. S12 NOT S13 Limiters - English Language

IV. Search strategy in Web of science

1. TS=(asthma*)

2. TS=(omalizumab) OR TS=(mepolizumab) OR TS=(reslizumab) OR TS=(benralizumab) OR TS=(dupilumab) OR TS=(tralokinumab) OR TS=(lebrikizumab) OR TS=(tezepelumab) OR TS=(brodalumab) OR TS=(ligelizumab) OR TS=(Pitrakinra)

3. TS=((biologic*) NEAR/1 (treatment* OR therap* OR medicine* OR drug* OR agent* OR product*)) OR TS=("monoclonal antibod*") OR TS=("biologic*")

4. TS=("responsive*") OR TS=("response") OR TS=("respond*") OR TS=("nonrespon*") OR TS=("outcome assessment*") OR TS=("treatment outcome*") OR TS=("meaningful change") OR TS=(Minimal* NEAR/1 (clinical* OR important OR real OR significant) NEAR/1 (change OR difference)) OR TS=(Minimal* NEAR/1 clinical* NEAR/1 (important OR significant) NEAR/1 (change OR difference)) OR TS=("MCID") OR TS=("MID") OR TS=("MIC")

5. #3 OR #2

6. (#1 AND #4 AND #5) NOT TS=("interview*") NOT TS=("focus group*") NOT TS=(narration) NOT TS=("qualitative research") NOT TI=(survey*)

7. #6 NOT TS=((("semi-structured" OR semistructured OR unstructured OR informal OR "in-depth" OR indepth OR "face-to-face" OR structured OR guide) NEAR/3 (interview* OR discussion* OR questionnaire*)) OR (focus group* OR qualitative OR ethnograph* OR fieldwork OR "field work" OR "key informant"))

8. (#7 NOT TS=((animal*) NOT (human* OR patient*))) AND LANGUAGE: (English)

9. (#7 NOT TS=((animal*) NOT (human* OR patient*))) AND LANGUAGE: (English)

Refined by: [excluding] DOCUMENT TYPES: (PROCEEDINGS PAPER OR EDITORIAL MATERIAL OR REVIEW OR MEETING ABSTRACT)

Appendix 3. Detailed methods

Data extraction, risk of bias assessment, quality, and synthesis of the results.

Data extraction was based on the COSMIN (COnsensus-based Standards for the selection of Measurement Instruments) guideline[1] for outcome measures. Data about study design; population characteristics and subgroups including sample size; asthma definition and severity; intervention and comparator (where appropriate); follow-up period; methodological approach to defining therapeutic response; definition of response and non-response (sole or composite outcome measures), development data, data on measurement properties (including: reliability (internal consistency, reliability, measurement error), validity (content, construct validity, responsiveness to change)) and characteristics of the outcome measurements were extracted into a template form independently by two reviewers (EK, AR). Any discrepancies were resolved by discussion or by a third reviewer (GR). The final extraction was cross-checked. Authors of included studies were contacted to provide additional data if needed.

Two reviewers (EK,AR) independently assessed the Risk of Bias (RoB) in individual studies using the COSMIN checklist for PROMs[2,3] and composite outcome measures (COSMIN RoB for non-Patient Reported Outcomes)[4]. Criterion validity was not evaluated as no gold standard exists in severe asthma.

First, development of the outcome measures was assessed based on relevance, comprehensiveness, and comprehensibility according to ten criteria.[3] Each criterion was rated as positive (+), negative (-), or indeterminate (?). The overall rating was provided as sufficient (+), insufficient (-), or inconsistent (±) which were based on the results from developmental and content validity studies as well as reviewers rating. If the developmental process for an outcome measure was not reported, then the overall rating was based only on the reviewer rating.

Second, we assessed RoB for each measurement property in the validation studies and rated it as very good, adequate, doubtful, or inadequate. The overall rating per measurement property was determined by the lowest rating for each standard.[1,2] The RoB assessment of response definitions was not undertaken as it is not part of the COSMIN RoB checklist.

Furthermore, we applied quality criteria. Each measurement property was rated as either sufficient (+), insufficient (-), or indeterminate (?) based on the predefined criteria for good measurement properties (GMP).[1] For construct validity and responsiveness, the review team formulated *a priori* hypotheses about the expected relationships between an outcome measure and comparator instruments. Overall, ≥75% of the results were expected to meet the criteria to be classified as sufficient.[1] Criteria for GMP are listed in **Table S2**.

Lastly, the certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[1,3,5] Quality of evidence was rated as 'high', 'moderate', 'low' or

'very low' for four factors (RoB, inconsistency, imprecision, and indirectness) for 'validity' studies while for 'developmental' studies rating was done according to three (RoB, inconsistency, and indirectness) by two reviewers (EK, AR). Papers describing development of the outcome measure were eligible for inclusion regardless of severity of asthma but subsequently downgraded for indirectness. Only inconsistency, imprecision and indirectness were assessed for the definitions of response as per the COSMIN guideline.[1] GRADE was not assessed in studies with indeterminate (?) rating based on GMP.[1] Any disagreements were resolved through the consultation with a third reviewer (GR). A descriptive synopsis with summary data tables were produced, and results were summarized using narrative synthesis.

Table S1. COSMIN definitions of domains, measurement properties, and aspects of measurement properties.

Term			Definition
Domain	**Measurement Property**	**Aspect of a Measurement Property**	
Reliability			The degree to which the measurement is free from measurement error
Reliability (extended definition)			The extent to which scores for patients who have not changed are the same for repeated measurement under several conditions: e.g. using different sets of items from the same health related-patient reported outcomes (HR-PRO; internal consistency); over time (test-retest); by different persons on the same occasion (inter-rater); or by the same persons (i.e. raters or responders) on different occasions (intra-rater)
	Internal consistency		The degree of the interrelatedness among the items
	Reliability		The proportion of the total variance in the measurements which is due to ''true'' differences between patients
	Measurement error		The systematic and random error of a patient's score that is not attributed to true changes in the construct to be measured
Validity			The degree to which an HR-PRO instrument measures the construct(s) it purports to measure
	Content validity		The degree to which the content of an HR-PRO instrument is an adequate reflection of the construct to be measured
		Face validity	The degree to which (the items of) an HR-PRO instrument indeed looks as though it is an adequate reflection of the construct to be measured
	Construct validity		The degree to which the scores of an HR-PRO instrument are consistent with hypotheses (for instance with regard to internal relationships, relationships to scores of other instruments, or differences between relevant groups) based on the assumption that the HR-PRO instrument validly measures the construct to be measured
		Structural validity	The degree to which the scores of an HR-PRO instrument are an adequate reflection of the dimensionality of the construct to be measured
		Hypotheses testing	Idem construct validity
		Cross-cultural validity	The degree to which the performance of the items on a translated or culturally adapted HR-PRO instrument are an adequate reflection of the performance of the items of the original version of the HR-PRO instrument
	Criterion validity		The degree to which the scores of an HR-PRO instrument are an adequate reflection of a ''gold standard''
Responsiveness			The ability of an HR-PRO instrument to detect change over time in the construct to be measured
	Responsiveness		Idem responsiveness
Interpretability			Interpretability is the degree to which one can assign qualitative meaning—that is, clinical or commonly understood connotations—to an instrument's quantitative scores or change in scores.

COSMIN, COnsensus-based Standards for the selection of health Measurement INstruments; HR PRO, health related-patient reported outcomes. Taken from Mokkink LB et al.[6]

Table S2. COSMIN criteria for good measurement properties.

Measurement property (definition)	Rating	Criteria
Structural validity	+	**CTT** CFA: CFI or TLI or comparable measure > 0.95 OR RMSEA < 0.06 OR SRMR < 0.08[a] **IRT/Rasch** No violation of unidimensionality[b]: CFI or TLI or comparable measure > 0.95 OR RMSEA < 0.06 OR SRMR < 0.08 AND no violation of local independence: residual correlations among the items after controlling for the dominant factor < 0.20 OR Q3's < 0.37 AND no violation of monotonicity: adequate looking graphs OR item scalability > 0.30 AND adequate model fit IRT: χ^2 > 0.001 Rasch: infit and outfit mean squares ≥ 0.5 and ≤ 1.5 OR Z-standardized values > −2 and < 2
	?	CTT: not all information for '+' reported IRT/Rasch: model fit not reported
	-	Criteria for '+' not met
Internal consistency	+	At least low evidence[c] for sufficient structural validity[d] AND Cronbach's alpha(s) ≥ 0.70 for each unidimensional scale or subscale[e]
	?	Criteria for "At least low evidence[c] for sufficient structural validity[d]" not met
	-	At least low evidence[c] for sufficient structural validity[d] AND Cronbach's alpha(s) < 0.70 for each unidimensional scale or subscale[e]
Reliability	+	ICC or weighted Kappa ≥ 0.70
	?	ICC or weighted Kappa not reported
	-	ICC or weighted Kappa < 0.70
Measurement error	+	SDC or LoA < MIC[d]
	?	MIC not defined
	_	SDC or LoA > MIC[d]
Hypotheses testing for construct validity	+	The result is in accordance with the hypothesis[f]
	?	No hypothesis defined (by the review team)
	-	The result is not in accordance with the hypothesis[f]
Responsiveness to change	+	The result is in accordance with the hypothesis[f] OR AUC ≥ 0.70
	?	No hypothesis defined (by the review team)
	-	The result is not in accordance with the hypothesis[f] OR AUC < 0.70

AUC, area under the curve; CFA, confirmatory factor analysis; CFI, comparative fit index; CTT, classical test theory; DIF, differential item functioning; ICC, intraclass correlation coefficient; IRT, item response theory; LoA, limits of agreement; MIC, minimal important change; RMSEA, root mean square error of approximation; SEM standard error of measurement; SDC, smallest detectable change; SRMR, standardized root mean residuals; TLI, Tucker–Lewis index. Taken from COSMIN, COnsensus-based Standards for the selection of health Measurement INstruments[1].

"+" = sufficient, "−" = insufficient, "?" = indeterminate

[a]To rate the quality of the summary score, the factor structures should be equal across studies

[b]Unidimensionality refers to a factor analysis per subscale, while structural validity refers to a factor analysis of a (multidimensional) patient reported outcome measure

[c]As defined by grading the evidence according to the GRADE approach

[d]This evidence may come from different studies

[e]The criteria 'Cronbach alpha < 0.95' was deleted, as this is relevant in the development phase of a PROM and not when evaluating an existing PROM

[f]The results of all studies should be taken together and it should then be decided if 75% of the results are in accordance with the hypotheses

Table S3. Approach to development of outcome measures.

Reference, year	Scale	Approach to development of outcome measurements
		Composite outcome measures
Fitzpatrick, 2020[7]	ASSESS	Adapted from the CASI by clinicians only: removed daytime symptoms and night time symptom dimensions and replaced with the total ACT score (weighted at 30%), modified ranges for FEV_1, medications, and length for assesment of exacerbations.
Wildfire 2012[8]	CASI	Developed by physicians only. 1. Determining independent dimensions of asthma severity via factor analysis. 2. Delphi exercise: clinical weighting of the dimensions of asthma severity. 3. Scale properties of the Composite Asthma Severity Index. 4. External validation.
De Llano, 2021[9]	FEOS	Developed by physicians only. 1. Systematic literature review. 2. Selection of domains and measurement tools: Delphi exercise. 3.Weighted of selected domains: multicriteria decision analysis. 4.Face validity.
		Asthma symptom outcome measures
Shen, 2021[10] Revicki, 1998[11]	ASUI	1. Literature review, patient interviews (including ranking order the relative importance of the items) and discussion with physicians. 2. Determination of a scoring algorithm using visual analog scale and standard gamble techniques, subsequently using multi-attribute utility function.
Shen, 2021[10]	ASI	Modified version of the ASUI which includes the 4 asthma symptoms, but excludes questions about assessment of medication side effects (eg, "how many days were you bothered by side effects of your asthma medication during the past 2 weeks?," "if 1 day or more what side effects did you have?," and "on average, how severe were the side effects of your asthma medication during the past 2 weeks?").
Globe, 2015 [12] Globe, 2019[13]	ASD	1. Concept elicitation interviews in 34 adults (38.9 years (13.0), 61.8% females, ACQ≥3 in 20.6%) and 16 adolescents (15.2 years (1.6), 56.3% males, ACQ≥3 in 31.3%) with clinical diagnosis of persistent asthma. 2. Cognitive interviews in 15 adults (30.7 years (9.7), 86.7% females, ACQ≥3 in 20.0%) and 9 adolescents (14.1 years (2.2), 77.8% males, ACQ≥3 in 11.1%) with a clinical diagnosis of persistent asthma.
		Asthma control outcome measures
Lloyd, 2007[14]	GETE	Developed by physicians only
		Asthma quality of life measures
Hyland, 2018[15]	SAQ	1. Identification of domains of an instrument. 2.Focus group to seek feedback about draft instrument: patient with severe asthma defined by BTS guideline (n=16) between 24-69 y.o; mean age of 47 (SD = 13.53); female (n=12).

ACQ, Asthma Control Questionnaire; BTS, British Thoracic Society; GETE, Global Evaluation of Treatment Effectiveness; ASSESS, Asthma Severity Scoring System; ASUI, Asthma Symptom Utility Index; ASI, Asthma Symptom Index; ASD, Asthma Symptom Diary; ACT, Asthma Control Test; CASI, Composite Asthma Severity Index; FEOS, FEV1, Exacerbations, Oral Corticosteroids, Symptoms Score; SAQ, Severe Asthma Questionnaire; NR, Not reported; FEV1, Forced Expiratory Volume in 1 second.

Table S4. Summary of characteristics of the outcome measures.

Instrument (year)	Mode of administration	(Sub)scale(s) (No. of Items)	Type of response categories	Intended context of use	Target population	Time to complete (minutes)	Patient/carer report	Original language
			Composite outcome measures					
Fitzpatrick, 2020[7] ASSESS	Interviewer administered, paper form (ACT[16-18]: self, at-home paper, phone, mail)	4 items: ACT (5 items), FEV_1, current medications, exacerbations.	Multiple choice questions	Clinical trials and routine clinical practice	Adolescents (≥12 years) and adults	Not reported (ACT: 2 min)	Patient and clinician	English
Wildfire,2012[8] CASI	Interviewer administered, paper form, online calculator available	5 domains: day symptoms and albuterol use, night symptoms and albuterol use, controller treatment, lung function measures, and exacerbations.	Multiple choice questions	Intervention studies and clinical practice	Children ≥ 6 years and adolescents*	Not reported	Patient and clinician	English
de Llano, 2021[9] FEOS	Paper (ACT[16-18] : self, at-home paper, phone, mail)	4-items (OCS, severe exacerbations, ACT, FEV_1)	Multiple choice questions	Clinical trials, patient monitoring	Adults	Not reported (ACT: 2 min)	Patient and clinician	English
			Asthma symptom outcome measures					
Revicki, 1998[11] ASUI	Interviewer administered, paper form	11 items [four symptoms (cough, wheeze, shortness of breath, and awakening at night) and two dimensions (frequency and severity] and side effect of medications	4-point Likert scale	Clinical trials and cost effectiveness studies	Adults	Not reported	Patient	English (for the USA). Italian, French
Shen, 2021[10] ASI	Interviewer administered, paper	8 items [four symptoms (cough, wheeze, shortness of breath, and awakening at night) and two dimensions (frequency and severity]	4-point Likert scale	Clinical trials, patient monitoring	Adults	Not reported	Patient	English, Italian, French
Globe,2015[12] ASD	Self-complete, electronic device	10-items (5 morning and 5 evening)	5-point Likert scale	Clinical research	Adolescents (≥ 12 years) and adults	Not reported	Patient	English
			Asthma control outcome measures					
Llyod, 2007[14] GETE	Interviewer administered, paper form	2 items	5-point Likert scale	Clinical trials and routine clinical practice	Adolescents and adults	Not reported	Patient and clinician	English
			Asthma quality of life measures					
Hyland, 2018[15] SAQ	Self-complete, paper form	SAQ: 16 items SAQ-global: 1 item	7-point Likert scale	Clinical research, patient monitoring	Adults 16–78 years (reading age 11-12 years)	3-6 minutes	Patient	English (UK), Portuguese

ACT, Asthma Control Test; ASUI, Asthma Symptom Utility Index; ASI, Asthma Symptom Index; ASD, asthma symptom diary; ASSESS, Asthma Severity Scoring System; CASI, Composite Asthma Severity Index; GETE, Global Evaluation of Treatment Effectiveness; SAQ, Severe Asthma Questionnaire. FEOS, FEV1, Exacerbations, Oral Corticosteroids, Symptoms Score; FEV_1, Forced Expiratory Volume in 1 second; OCS, Oral Corticosteroids. *CASI is also validated in adults with asthma based on a conference abstract.[19]

Table S5. Summary of data for measurement properties of outcome measures.

Reference, year	Construct validity**	Reproducibility	Internal consistency	Responsiveness
Lloyd, 2007[14] GETE	1.Spearman rank-order correlation between GETE and AQLQ (physician GETE / patient GETE)*: • Activities score: –0.29 / –0.32 • Change from baseline in activities score: –0.35 / –0.37 • Emotions score: –0.36 / –0.37 • Change from baseline in emotions score: –0.31 / –0.35 • Environmental exposure score:–0.25 / –0.26 • Change from baseline in environmental exposure score: –0.27 / –0.30 • Symptom score –0.40 / –0.45 • Change from baseline in symptom score: –0.36 / –0.39 • Overall score: –0.38 /–0.41 • Change from baseline in overall score: –0.38 /–0.41 * All correlations were p<0.0001. 2. Spearman rank-order correlation between GETE and clinical characteristics (physician GETE / patient GETE)*: • Actual FEV1 value: –0.20/–0.14 • Total asthma symptom score: 0.32/ 0.34 • Change in total asthma symptom score: 0.26/ 0.31 • Nocturnal symptom score: 0.22/ 0.22 • Change in nocturnal symptom score: 0.21/ 0.23 • Daytime symptom score: 0.31/ 0.34 • Change in daytime symptom score: 0.24/ 0.29 • No. of puffs of rescue medication/day: 0.33 /0.33 • Change in no. of puffs of rescue medication/day: 0.26/ 0.29 * All correlations were p<0.0001. 3. Actual mean FEV1 (SD)/ mean total asthma symptom score (SD)/ mean nocturnal symptom score (SD) / mean daytime symptom score (SD) / mean n on puffs of rescue meds (SD)	NA	NA	NA

Reference, year	Construct validity**	Reproducibility	Internal consistency	Responsiveness
	Patient version • Complete control of asthma: 2.20 (824.58) / 1.49 (1.58) / 0.50 (0.63) / 0.68 (0.71) / 3.23 (4.49) • Marked improvement of asthma: 2.12 (776.94) / 2.14 (1.85) / 0.69 (0.81) / 1.02 (0.86) / 3.76 (4.99) • Discernible, but limited improvement in asthma: 2.07 (761.41) / 2.70 (1.99) / 0.91 (0.96) / 1.38 (0.98) / 5.47 (6.84) • No appreciable change in asthma: 2.03 (838.37) / 2.98 (2.21) / 1.01 (1.09) / 1.48 (1.05) / 5.20 (5.20) • Worsening of asthma: 1.82 (691.97) / 5.38 (3.39) / 2.06 (1.34) / 2.32 (1.46) / 13.23 (7.83) p values per clinical indicator: 0.37/ 0.0091/ <0.0001/ <0.0001/ 0.0002/ 0.0016 / < 0.0001 / 0.0009 / 0.0002 *Physician version* • Complete control of asthma: 2.37 (877.81) / 1.68 (1.73)/ 0.64 (0.70) / 0.74 (0.75) / 3.13 (4.17) • Marked improvement of asthma: 2.15 (790.23) / 2.01 (1.83) / 0.61 (0.81) / 1.00 (0.88) / 3.65 (5.66) • Discernible, but limited improvement in asthma: 2.08 (751.92) / 2.61 (1.90) / 0.83 (0.87)/ 1.27 (0.90)/ 4. 93 (5.66) • No appreciable change in asthma: 1.95 (751.86) / 3.15 (2.34) / 1.15 (1.13) / 1.58 (1.12) / 6.35 (5.98) • Worsening of asthma: 1.66 (445.85)/ 6.41 / 1.38 (1.95) / 2.63 / 16.12 (11.49) P values per clinical indicator: 0.0091; < 0.0001/ 0.0016/ <0.0001/ 0.0002 4. Data presented per GETE level by AQLQ mean activity score (SD)/Mean emotions score (SD) /Mean environment score (SD) / Mean symptoms score (SD) / Mean overall score (SD) *Patient version GETE* • Complete control of asthma: 5.74 (1.21) / 5.83 (1.19) / 5.52 (1.37) / 5.75 (1.07) / 5.73 (1.07)			

Reference, year	Construct validity**	Reproducibility	Internal consistency	Responsiveness
	• Marked improvement of asthma: 5.15 (1.21) / 5.29 (1.30) / 4.89 (1.34) / 5.15 (1.08) / 5.13 (1.06) • Discernible, but limited improvement in asthma: 4.76 (1.25) / 4.72 (1.43) / 4.56 (1.43) / 4.58 (1.13) / 4.64 (1.12) • No appreciable change in asthma: 4.45 (1.33) / 4.33 (1.47) / 4.43 (1.35) / 4.22 (1.17) / 4.31 (1.10) • Worsening of asthma: 4.40 (1.47) / 3.88 (1.57) / 4.33 (1.55) / 3.76 (1.24) / 4.03 (1.19) *Physician version GETE* • Complete control of asthma: 5.73 (1.22) / 5.85 (1.17) / 5.50 (1.38) / 5.72 (1.05) / 5.71 (1.06) • Marked improvement of asthma: 5.21 (1.25) / 5.38 (1.27) / 4.99 (1.35) / 5.23 (1.09) / 5.20 (1.07) • Discernible, but limited improvement in asthma: 4.79 (1.26) / 4.72 (1.49) / 4.59 (1.42) / 4.60 (1.21) / 4.67 (1.17) • No appreciable change in asthma: 4.56 (1.29) /4.54 (1.42) /4.48 (1.40) /4.37 (1.16) /4.45 (1.09) Worsening of asthma: 4.42 (1.40)/ 3.29 (1.32) /4.04 (1.46) / 3.70 (1.00) / 3.90 (1.10)			
Fitzpatrick, 2020[7] ASSESS	• AQLQ total score: r= -0.315** • AQLQ symptom: r= -0.387** • AQLQ activity: r= -0.244* • AQLQ emotion: r= -0.387** • AQLQ environment: r= -0.253* *P < .05 and **P < .01.	ICC (baseline/ 12mo; 12mo/24 mo; 24mo/36 mo) • *Entire sample* 0.764/ 0.768/ 0.813 • *12-17 ys*: 0.717/ 0.841/ 0.732 • *>18 y:* 0.768 / 0.766/ 0.816	Cronbach's alpha: *entire sample* 0.639 *12-17y:* 0.468 *≥18 y:* 0.662	1. r values: AQLQ total score / symptom / activity / emotion / environment: • *0-12 mo:* -0.550* / -0.579* / -0.453* / -0.488* / -0.300* • *12 - 24 mo:* -0.462* / -0.508* / -0.349* / -0.408* / -0.212* • *24 - 36 mo:* -0.468* / -0.481* / -0.396* / -0.368* / -0.265* *P < .001. 2. r values for changes: 0 and 12 months / 12 and 24 months/ 24 and 36 months: • Change in ASSESS vs Change in ACT: -0.668* / -0.676* / -0.622

Reference, year	Construct validity**	Reproducibility	Internal consistency	Responsiveness
				• Change in ASSESS vs Change in FEV1 absolute % difference: -0.395* / -0.369* / -0.372*.
Wildfire, 2012[8] CASI*				Intervention group showed improvement in CASI & symptom days (0.67 points & 0.48-day improvement; both P < .001). CASI: 32% greater magnitude of improvement (standardized effect size: 0.25 vs 0.17 for symptom days)
Shen, 2021[10] ASUI	1.ASUI baseline/ week 12: SGRQ score: -0.68 / -0.72 SGRQ Symptom: -0.78 / -0.81 SGRQ Impact: -0.46 / -0.56 SGRQ Activity: -0.60 / -0.66 ACQ-5 score: -0.78 / -0.85 EQ-5D index score: 0.51 / 0.52 EQ-5D VAS score: 0.44 / 0.56 % FEV1 pred.: 0.19 / 0.28 FEV1 (mL): 0.15 / 0.20 No. of exacerbations: -0.15 / -0.29 Global rating of activity limitation: -0.43 / -0.51 ASD Score: -0.54 / -0.53 2.Known group validity: Group with higher ACQ-5 scores (≥1.5 indicating poorly controlled asthma) tended to have lower ASUI scores (indicative of greater symptom burden) (p<0.0001). For % pred FEV1, group with lowest FEV1 function (≤ 60%) had the lowest ASUI scores (p<0.0001).	ICC=0.87-0.90	Cronbach's alpha: Baseline=0.87 Week 12 =0.90	1.ASUI change from baseline to week 4: ΔACQ-5 score: - 0.57 ΔSGRQ score: 0.50 ΔSGRQ Symptom: -0.53 ΔSGRQ Impact: -0.25 ΔSGRQ Activity: -0.41 Δ % predicted FEV1: 0.16 No. of asthma exacerbations during on-treatment phase: -0.02 2. ASUI change from baseline to week 12: ΔACQ-5 score: -0.67 ΔSGRQ score: -0.60 ΔSGRQ Symptom: -0.67 ΔSGRQ Impact: -0.42 ΔSGRQ Activity: -0.50 Δ % predicted FEV1: 0.25 No. of asthma exacerbations during on-treatment phase: -0.05
Shen, 2021[10] ASI	1.ASI (baseline/week 12): SGRQ score: 0.67/ 0.71 SGRQ Symptom: 0.80 / 0.82	ICC=0.87-0.90	Cronbach's alpha:	1.ASI change from baseline to week: 4: ΔACQ-5 score: 0.58

Reference, year	Construct validity**	Reproducibility	Internal consistency	Responsiveness
	SGRQ Impact: 0.46 / 0.55 SGRQ Activity: 0.59 / 0.65 ACQ-5 score: 0.79 / 0.85 EQ-5D index score: -0.49/ -0.49 EQ-5D VAS score: -0.43/ -0.55 % FEV1 pred.: -0.20/ -0.28 FEV1 (mL): -0.14/ -0.19 No. of exacerbations: 0.12 / 0.28 Global rating of activity limitation: 0.43 / 0.49 ASD Score: 0.54 / 0.52 / 2. Known group validity: Group with higher ACQ-5 scores (≥1.5 indicating poorly controlled asthma) tended to have higher ASI scores (p<0.0001). For % pred FEV1, group with lowest FEV1 function (≤60%) had the highest ASI scores (p<0.0001).		Baseline=0.89, Week 12=0.93	ΔSGRQ score: 0.50 ΔSGRQ Symptom: 0.55 ΔSGRQ Impact: 0.27 ΔSGRQ Activity: 0.39 Δ % predicted FEV1: -0.18 No. of asthma exacerbations during on-treatment phase: 0.05 2.ASI change from baseline to week 12: ΔACQ-5 score: 0.69 ΔSGRQ score: 0.61 ΔSGRQ Symptom: 0.70 ΔSGRQ Impact: 0.45 ΔSGRQ Activity: 0.49 Δ % predicted FEV1: -0.28 No. of asthma exacerbations during on-treatment phase*: 0.09
Hyland, 2018[20] Masoli, 2021[21] Lanario, 2021[22] SAQ	1. SAQ vs miniAQLQ =0.76; ACT=0.68; EQ-5D-5L score=−0.76; EQ-5D-VAS= 0.71; SAQ-global scale= 0.72; FEV1 % predicted=0.27; BMI=−0.31 2. SAQ-global vs MiniAQLQ= 0.71; ACT total= 0.68; EQ-5D-5L= −0.71; EQ-5D-VAS= 0.76; FEV1 % predicted=0.26; BMI=−0.22 3. Data for FEV1% predicted vs SAQ domains: SAQ score: 0.23; SAQ My Life: 0.29; SAQ My Mind: 0.15; SAQ My Body: 0.15; SAQ global score: 0.28 4.Data for cumulative prednisolone vs SAQ domains: SAQ score: -0.34; SAQ My Life: − 0.35; SAQ My Mind: − 0.23; SAQ My Body: − 0.34; SAQ global score: − 0.37 5.Data for Exacerbations in the last 12 mo requiring OCS vs SAQ domains:	ICC= 0.93 (SAQ) ICC= 0.93 (SAQ-global)	Cronbach's alpha= 0.93.	Change scores for different degrees of global rating of change is available for SAQ, SAQ subscales and SAQ-global.

Reference, year	Construct validity**	Reproducibility	Internal consistency	Responsiveness
	SAQ score: -0.37; SAQ My Life: − 0.37; SAQ My Mind: − 0.33; SAQ My Body: − 0.33; SAQ global score: − 0.36 6. Data for Hospital admissions in the last 12 mo vs SAQ domains: SAQ score: -0.17; SAQ My Life: − 0.16; SAQ My Mind: − 0.16; SAQ My Body: − 0.13; SAQ global score: − 0.23 7. EQ-5D-5L Index value/EQ-5D-5L item 5–Anxiety and Depression/EQ-5D VAS/ ACQ score/ACT total SAQ score:0.72/ -0.64 /0.73/ -0.75/0.71 SAQ My Life: 0.73/-0.54/0.74/-0.79/0.72 SAQ My Mind: 0.64/-0.73/0.63/ -0.62/ 0.62 SAQ My Body: 0.59/-0.56/0.62/-0.60/ 0.64 SAQ global score: 0.66/-0.50/ 0.79/ 0.77/ 0.68			
Globe, 2019[13] ASD				1. Responsiveness of the Average 7-Day ASD Score at Weeks 12 and 24 Data presented for Responders Mean (SE) Non-Responders/ Mean (SE) Difference P-Value. Effect size presented for responder / nonresponder Week 12 ACQ > 0.5: −0.49 (0.03) / 0.05 (0.03).Effect size: 0.82 / 0.08 ACQ > 1.0: −0.54 (0.03) / −0.13 (0.03).Effect size: 0.90 / 0.22 PGA: −0.48 (0.03) / −0.07 (0.03) Effect size: 0.80 / 0.12 Week 24: ACQ > 0.5: −0.59 (0.03) / −0.06 (0.03) / − 0.53. Effect size: 0.98 / 0.10 ACQ > 1.0: −0.68 (0.04) / −0.15 (0.03) / − 0.53.Effect size: 1.13 / 0.25

Reference, year	Construct validity**	Reproducibility	Internal consistency	Responsiveness
				PGA: −0.60 (0.03) / −0.10 (0.04) / −0.49.Effect size: 1.00 / 0.17 2. Responsiveness of ASD Symptomatic Days in a 7-Day Period at Weeks 12 and 24 Data presented for Responders Mean (SE) Non-Responders Mean (SE).Effect size presented for responder / nonresponder: Week 12: ACQ > 0.5: −2.21 (0.16) / −0.57 (0.18).Effect size: 0.73 / 0.19 ACQ > 1.0: −2.35 (0.20) / −0.90 (0.16).Effect size: 0.78 / 0.30 PGA: −2.34 (0.16) / −0.45 (0.17) Effect size 0.78 / 0.15 Week 24: ACQ > 0.5: −2.86 (0.18) / − 0.28 (0.28).Effect size 0.95 / 0.09 ACQ > 1.0: −3.21 (0.21) / −0.77 (0.20).Effect size 1.07 / 0.26 PGA: −2.97 (0.19) / −0.45 (0.23) Effect size 0.99 / 0.15 3. Spearman correlations between baseline to 12-week changes in ASD scores and baseline to 12-week changes in ACQ and PGA scores were 0.59 and 0.57, respectively. 4. Correlations between baseline to 24-week changes in ASD scores and

Reference, year	Construct validity**	Reproducibility	Internal consistency	Responsiveness
				baseline to 24-week changes in ACQ and PGA scores were 0.67 and 0.53, respectively.

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; ASSESS, Asthma Severity Scoring System; ASUI, Asthma Symptom Utility Index; ASI, Asthma Symptom Index; ASD, Asthma Symptom Diary; BMI, Body Mass Index; CASI, Composite Asthma Severity Index; EQ-5D-5L,EuroQol Questionnaire-5 Dimensions-5 Levels; EQ-5D-VAS, EuroQol Questionnaire-5 Dimensions Visual Analogue Scale; GETE, Global Evaluation of Treatment Effectiveness; FEV1, forced expiratory volume in 1 second; ICC, intraclass correlation coefficient; miniAQLQ, mini- Asthma Quality of Life Questionnaire; PGA, Patient's Global Assessment; SAQ, Severe Asthma Questionnaire; SGRQ, St George's Respiratory Questionnaire. *Only external validation data was used for analysis as it was performed in a study with biologics. **As there is no golden standard in asthma, data about criterion validity was combined with construct validity.

Table S6. Additional study characteristics for validation studies.

Reference, year	Scale	Study design	N	Age (years) Mean (IQR)	Patient characteristics	Asthma severity (severe %)	Definition of asthma	Biological drug
Hyland, 2018[20]	SAQ	Observational	160	51	F=66%; FEV_1 % predicted=72 (28–137)	Severe (100%)	ERS/ATS guidelines	Omalizumab =21% Mepolizumab=3%
Lanario, 2021[22]	SAQ	Cross-sectional	460	51 (50–53)	F=65%; FEV_1 % predicted, mean (CI): 71.75 (69.79–73.71) Prescribed maintenance OCS, n (%): 218 (47)	Severe (100%)	ERS/ATS guidelines	Different biologics=39%
Wildfire, 2012[8]*	CASI	RCT	419	10.8 (8-14)	F= 42%; FEV_1 % predicted (mean ± SD) = 92.1±17.1	Mild to severe (54%)	Physician-diagnosis of asthma	Omalizumab=50%

ATS, American Thoracic Society; CASI, Composite Asthma Severity Index; ERS, European Respiratory Society; FEV1, forced expiratory volume in 1 second; F, females; SAQ, Severe Asthma Questionnaire; IQR, interquartile range; CI, confidence interval; SD, standard deviation; OCS, oral corticosteroids; RCT, Randomised Control Trial. *Only external validation data was used for analysis as it was performed in a study with biologics.

Table S7. Risk of bias assessment.

	ASSESS [7]	CASI[8]*	FEOS[9]	ASUI[10,11]	ASI[10]	ASD[12,13]	GETE[14]*	SAQ[15,20-22]**
PROM development	I	I	I	D	I	D	I	V
Structural validity								
Internal consistency	I			D	V			
Cross-cultural validity								
Reliability	I			A	A			A
Measurement error	I			A	A			
Construct validity	A			D	D		V	D
Responsiveness	D	V		D	A	D		D

ASSESS, Asthma Severity Scoring System; ASUI, Asthma Symptom Utility Index; ASI, Asthma Symptom Index; ASD, Asthma Symptom Diary; CASI, Composite Asthma Severity Index; GETE, Global Evaluation of Treatment Effectiveness; FEOS, FEV1, Exacerbations, Oral Corticosteroids, Symptoms Score; SAQ, Severe Asthma Questionnaire. *Only external validation data was used for analysis as it was performed in a study with biologics. Risk of bias in individual studies was investigated using the COSMIN checklist for PROMs[2,3] and composite outcome measures (COSMIN RoB for non-PROMs)[4]. V= very good; A = adequate; D = doubtful; I = inadequate. ** SAQ is based on a formative model; therefore, there was no need to investigate the internal consistency. Empty cells indicate that the measurement property was not investigated.

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My contribution: Together with my supervisor G. Roberts, I developed a concept and methodology for this study. I led preparation for the ethics application including drafting of the recruitment materials and patient information sheets. I recruited participants and conducted training calls with HCPs and patient advocates. I developed patient profiles and set up all surveys. I have conducted statistical analysis with my supervisor and drafted tables and figures. Lastly, synthesised the evidence and wrote first draft of the manuscript.

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

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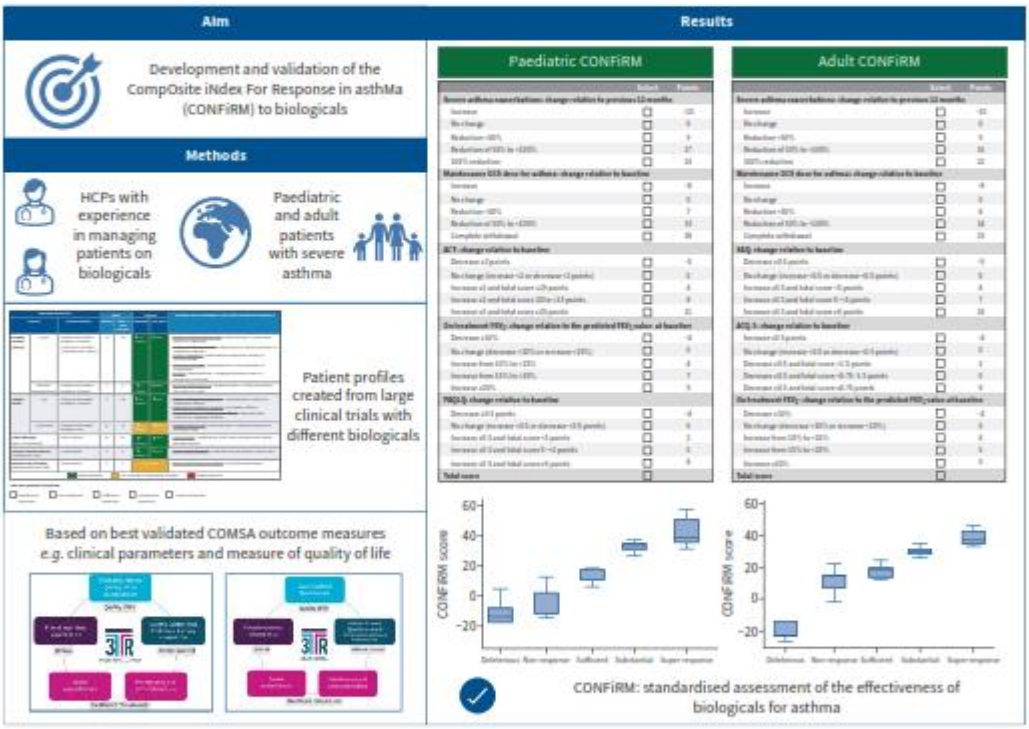

GRAPHICAL ABSTRACT Overview of the study. OCS: oral corticosteroid; ACT: Asthma Control Test; FEV_1: forced expiratory volume in 1 s; PAQLQ: Paediatric Asthma Quality of Life Questionnaire; ACQ-5: Asthma Control Questionnaire-5.

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

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Shareable abstract (@ERSpublications)
CONFiRM is a novel patient-centred measure of overall response to biological therapies in severe asthma. It shows good external validity and discriminative ability and is likely to be a valuable tool in assessing the effectiveness of biologicals in children and adults. https://bit.ly/3ZLkPEV

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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 biological therapies 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.

Methods International expert healthcare professionals 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 healthcare professionals evaluated CONFiRM's external validity.

Results Five levels of change for each COMSA outcome were agreed. Severe exacerbations and maintenance oral corticosteroid use were rated as the most important in determining both paediatric and

adult CONFiRM scores. There was strong agreement between healthcare professionals and patients, although patients assigned greater importance to quality of life. The CONFiRM score quantified response to a biological therapy from −31 (deterioration) to 69 (best possible response). Paediatric and adult CONFiRMs had good discriminative ability for a sufficient (area under the curve ⩾0.92) and a substantial (area under the curve ⩾0.95) response to biologicals. 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 that include quality of life measures. CONFiRMs should allow a more holistic understanding of response for the patient and a standardised assessment of the effectiveness of biologicals 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 asthma [1] and is associated with impaired quality of life (QoL), frequent severe asthma exacerbations and hospitalisations [2]. Biological therapies such as omalizumab, dupilumab, tezepelumab, benralizumab, dupilumab, reslizumab and mepolizumab are currently available for patients whose asthma remains uncontrolled despite adherence to maximum conventional asthma treatment. The effectiveness of biologicals 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 biologicals 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 or 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 biologicals are based on expert opinion, were 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 responses and identifying biomarkers of response to therapy in current clinical trials are 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 s (FEV_1), frequency of severe asthma exacerbations [13] and maintenance oral corticosteroid (OCS) 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 (C-ACT) [18, 19], while the adult COMSA includes the Severe Asthma Questionnaire [20, 21] and the Asthma Control Questionnaire-6 (ACQ-6) [22, 23].

In this study we aimed to develop the patient-centred, valid CompOsite iNdexes For Response in asthMa (CONFiRM) to biologicals for children and adults. A composite index is important because it facilitates standardised evaluation of an overall patient response, especially when the response 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 biologicals, 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 the relative importance of each COMSA outcome measure for the overall response in the paediatric and adult CONFiRM using multicriteria decision analysis (MCDA) [24]; 3) assess the 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 patients with severe asthma receiving biologicals 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

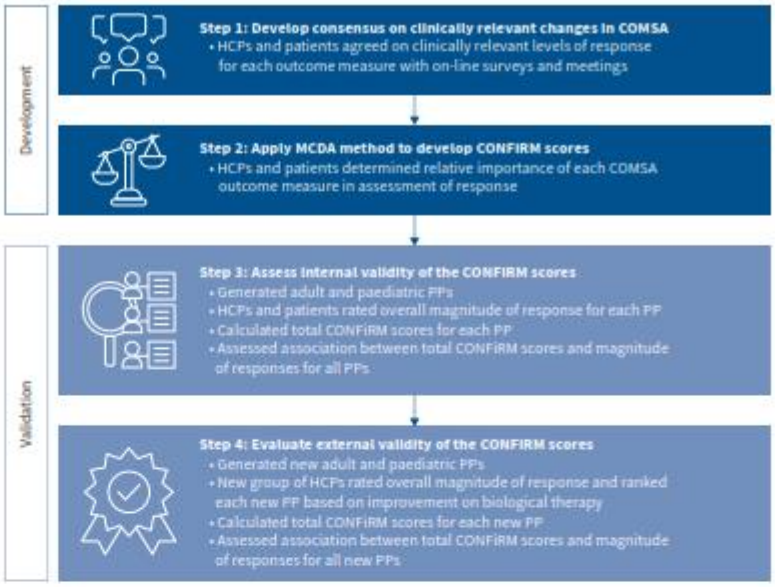

FIGURE 1 Flow diagram of the study. Words in italics indicate differences between steps.COMSA: Core Outcome Measures for Severe Asthma; CONFIRM: CompOsite INdex For Response in asthMa; HCP: healthcare professional; MCDA: multicriteria decision analysis; PP: patient profile.

receiving biologicals. The definition of severe asthma was based on the European Respiratory Society (ERS)/American Thoracic Society (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 step 4. Details of participant training are provided in supplementary 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 (supplementary appendix 2).

Step 2: Apply MCDA method to develop CONFIRM scores

An MCDA method was used to determine the 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 a better response to a biological (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 was 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 (supplementary 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 (supplementary table S1). A clustering algorithm was used to group together patient profiles with similar patterns of response to biologicals (supplementary appendix 4).

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	Maintenance OCS dose for asthma
Complete withdrawal	**Reduction <50%**
SAQ	SAQ
Increase ≥0.5 points and total score <5 points	**Increase ≥0.5 points and total score ≥6 points**
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 1 year after biological treatment
COMSA		Characteristics	Before	After 1 year therapy	Absolute	Per cent	
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 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 and 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 score=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 six attacks a year to two
Regular oral steroids, prednisolone dose (mg)		• None=better	0	0	No change		• Regular oral steroids for asthma - not treated with them

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 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 the European Respiratory Society/American Thoracic Society guideline [13]. Maintenance (regular) oral corticosteroid (OCS) use is defined as daily or alternate day use of OCS. SAQ: Severe Asthma Questionnaire; COMSA: Core Outcome Measures for Severe Asthma; ACQ: Asthma Control Questionnaire; FEV_1: forced expiratory volume in 1 s.

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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 the 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 response, substantial response or super-response (box 1, supplementary 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 the intraclass correlation coefficient (ICC) (appendix 6) [37].

Calculating total CONFiRM score for each patient profile

The overall CONFiRM score for each paediatric patient profile was calculated using the 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. A 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 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 (supplementary appendix 7). A similar approach to step 3 was used (figure 1). Additionally, participants ranked these new patient profiles from worsening to largest improvement after taking a biological. 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.

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 clinically 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; *e.g.* 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 (supplementary appendix 5).

Sample size and other statistical considerations

Data were analysed using STATA software version 16.1 (StataCorp LLC, College Station, TX, USA). The study sample size for stages 1–3 was calculated based on precision in estimating the 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 maintenance OCS at baseline. For all analyses, a p-value of <0.05 was considered statistically significant. See appendix 8 for more details.

RESULTS

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

A total of 69 participants (40 HCPs (58.0%), 29 patient advocates (42.0%)) completed the adult surveys and 72 (40 HCPs (55.6%), 32 patient advocates (44.4%)) the paediatric surveys (supplementary table S2). Consensus was reached for levels of response for each outcome measure (tables 1 and 2, supplementary table S3).

Step 2: Apply MCDA method to develop CONFiRM scores

The same group of participants took part in step 2 (supplementary table S4). Participants assigned the highest relative importance to severe asthma exacerbations and maintenance OCS in both adult and paediatric CONFiRMs (tables 1 and 2, supplementary figure S1). Weightings were similar for patient advocates and HCPs, except that patient advocates rated asthma-specific QoL higher than HCPs (figure 3, supplementary tables S5 and S6). Most participants gave the same answer for two repeated patient profiles (54 participants (81.8%) and 49 participants (77.8%) for paediatric and adult, respectively). Further details are in supplementary tables S7–11 and supplementary figure S2.

Step 3: Assess internal validity of CONFiRM scores

The patient profiles used in this step are summarised in supplementary table S12. A total of 146 participants took part: 79 (45 HCPs (57.0%), 34 patient advocates (43.0%)) reviewed the adult profiles and 67 (44 HCPs (65.7%), 23 patient advocates (34.3%)) reviewed the paediatric profiles (supplementary table S13). Patient advocates and HCPs appeared to classify responses for each patient profile similarly (supplementary figure S3). Agreement on assigned overall magnitude of response for repeated profiles was moderate for individual participants for the adult patient profiles (supplementary table S14). Agreement was also moderate for HCPs 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, supplementary table S15). Similar results were found for patient profiles where maintenance OCS was not used at baseline (supplementary 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 (AUC 0.95, 95% CI 0.95–0.96) CONFiRM. This was also the case for sufficient response (supplementary figures S5 and S6) plus for HCPs and patient advocates, whether on or off maintenance OCS at baseline, and in the additional bootstrap analysis to minimise the impact of overfitting (supplementary table S16).

There was a 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 $p<0.001$) (supplementary figure S7). The adult CONFiRM also showed good discrimination for super-responders as per the Delphi definition (AUC 0.93, 95% CI 0.92–0.94, $p<0.001$) (supplementary figure S8) [9].

A total of 75 participants attended the stakeholder meetings, including 48 HCPs (64.0%), 19 patient advocates (25.3%), five pharmaceutical representatives (6.7%), two health regulators (2.7%) and one representative from the 1000minds team (1.3%). Several comments for improvement of the CONFiRM tools were suggested and implemented (supplementary 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 (supplementary 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 (supplementary table S19). ICCs for repeated profiles were 0.59 and 0.65 for paediatric and 0.12 and 0.70 for adult profiles, demonstrating mostly moderate agreement (supplementary table S20).

Again, there was a clear relationship between the CONFiRM score for each patient profile and overall magnitude of change (figure 5, supplementary table S21) as we found in step 3 (figure 4). Similar results were found for adult patient profiles where maintenance OCS was not used at baseline (supplementary figure S9). Additionally, the composite measures had excellent discriminative ability for both substantial and sufficient responses (supplementary figure S10). Lastly, ranking of 15 cases in order of improvement after taking a biological 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 biological therapies for children and adults. We employed a rigorous methodology to quantify the overall

TABLE 1 Paediatric CompOsite iNdex For Response in asthMa (CONFiRM)

	Select	Points
Severe asthma exacerbations [8]: change relative to previous 12 months		
Increase[#]	☐	−10
No change[¶]	☐	0
Reduction <50%	☐	9
Reduction of 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 of 50% to <100%	☐	13
Complete withdrawal[f]	☐	18
ACT: change relative to baseline		
Decrease ⩾2 points [27]	☐	−5
No change (increase <2 or decrease <2 points)	☐	0
Increase ⩾2 and total score ⩽19 points [16]	☐	4
Increase ⩾2 and total score 20 to <23 points [27]	☐	8
Increase ⩾2 and total score ⩾23 points	☐	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 and total score <5 points	☐	2
Increase ⩾0.5 and total score 5–<6 points	☐	5
Increase ⩾0.5 and total score ⩾6 points	☐	8
Total score		☐

Calculation of CONFiRM scores: Points are assigned for the change in each Core Outcome Measures sets for paediatric and adult Severe Asthma (COMSA) outcome measure. Higher scores indicate better response to a biological; 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 the European Respiratory Society/American Thoracic Society guideline [13]. Maintenance OCS use is defined as daily or alternate day use of OCS. Childhood-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. OCS: oral corticosteroids; ACT, Asthma Control Test; FEV_1: forced expiratory volume in 1 s; PAQLQ: Paediatric Asthma Quality of Life Questionnaire. [#]: 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]; [+]: 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; [f]: low dose of maintenance OCS for adrenal insufficiency should be treated as withdrawal of maintenance oral corticosteroid [8]; [**]: change in on treatment FEV_1 is calculated as [(follow-up FEV_1 minus baseline FEV_1 divided by predicted FEV_1 value)×100] [26]. FEV_1 % predicted is being used rather than z-score only because this was more comprehensible to patient advocates participating in the project.

TABLE 2 Adult CompOsite iNdex For Response in asthMa (CONFiRM)

	Select	Points
Severe asthma exacerbations [8]: change relative to previous 12 months		
Increase[#]	☐	−10
No change[¶]	☐	0
Reduction <50%	☐	9
Reduction of 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 of 50% to 100%	☐	14
Complete withdrawal[f]	☐	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 and total score <5 points	☐	4
Increase ⩾0.5 and total score 5–<6 points	☐	7
Increase ⩾0.5 and total score ⩾6 points	☐	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 and total score >1.5 points [29]	☐	3
Decrease ⩾0.5 and total score >0.75–1.5 points	☐	6
Decrease ⩾0.5 and total score ⩽0.75 points [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 CONFiRM scores: Points are assigned for the change in each Core Outcome Measures sets for paediatric and adult Severe Asthma (COMSA) outcome measure. Higher scores indicate better response to a biological; 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 the European Respiratory Society/American Thoracic Society guideline [13]. Maintenance OCS use is defined as daily or alternate day use of OCS. [#]: 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]; [+]: 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; [f]: low dose of maintenance OCS for adrenal insufficiency should be treated as withdrawal of maintenance oral corticosteroid [8]; [##]: change in on treatment FEV_1 is calculated as [(follow-up FEV_1 minus baseline FEV_1 divided by predicted FEV_1 value)×100] [26]. FEV_1 % predicted is being used rather than z-score only because this was more comprehensible to patient advocates participating in the project. OCS: oral corticosteroids; SAQ: Severe Asthma Questionnaire; ACQ: Asthma Control Questionnaire; FEV_1: forced expiratory volume in 1 s.

response to biologicals, and because we involved 147 expert HCPs and patient advocates from more than 25 countries, the CONFiRM 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 biologicals 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 higher 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 biologicals. Lastly, external validity of the CONFiRMs provided similar results to internal validation.

Other composite definitions of response to biologicals, such as FEOS [8], and the super-responder [9] definition were developed only by clinicians and only for adult patients. This contrasts with the in-depth

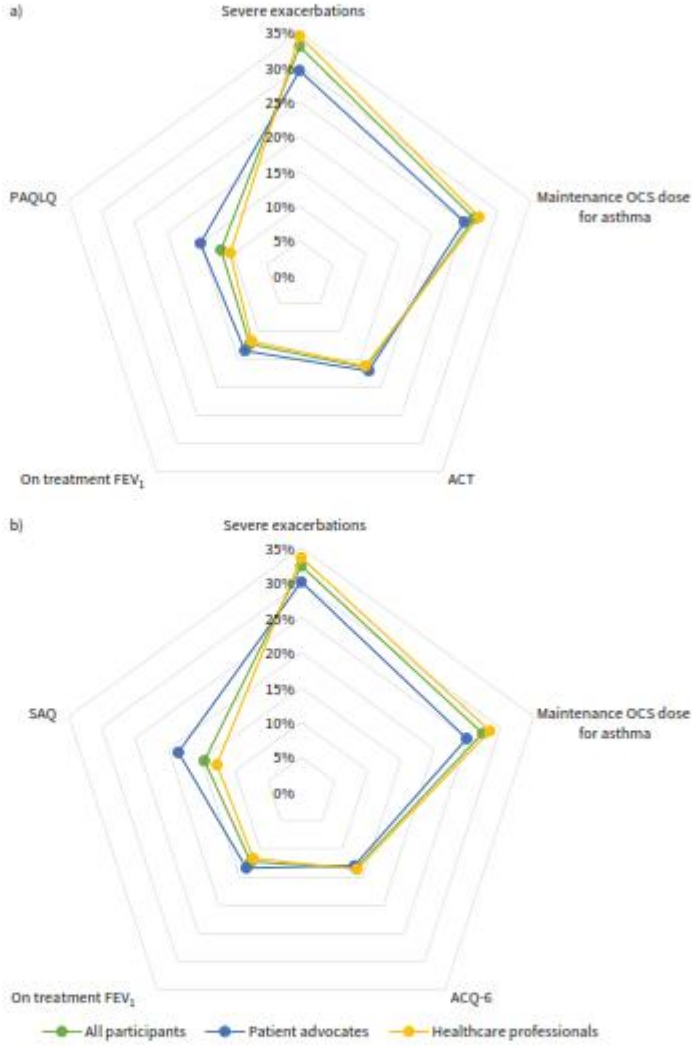

FIGURE 3 Maximal weights for each core outcome measure in the CompOsite iNdex For Response in asthMa (CONFIRMs). a) Paediatric CONFIRM. b) Adult CONFIRM. Spider plots describe the maximal mean weight assigned to Core Outcome Measures set for paediatric and adult Severe Asthma (COMSA) [12] outcome measure. The panel assumed that Asthma Control Test (ACT) and Childhood-ACT have the same weighting in the paediatric CONFIRM. Severe asthma attacks are defined as per the European Respiratory Society/American Thoracic Society guideline [13]. Maintenance oral corticosteroid (OSC) use is defined as daily or alternate day use of OCS. PAQLQ: Paediatric Asthma Quality of Life Questionnaire; FEV_1: forced expiratory volume in 1 s % predicted; SAQ: Severe Asthma Questionnaire; ACQ: Asthma Control Questionnaire.

public and patient involvement in CONFIRM throughout its development, conduct and interpretation of findings. People with severe asthma have the greatest stake in identifying which treatment "works" for them; by excluding their voices in defining response, the research community risks overlooking factors that

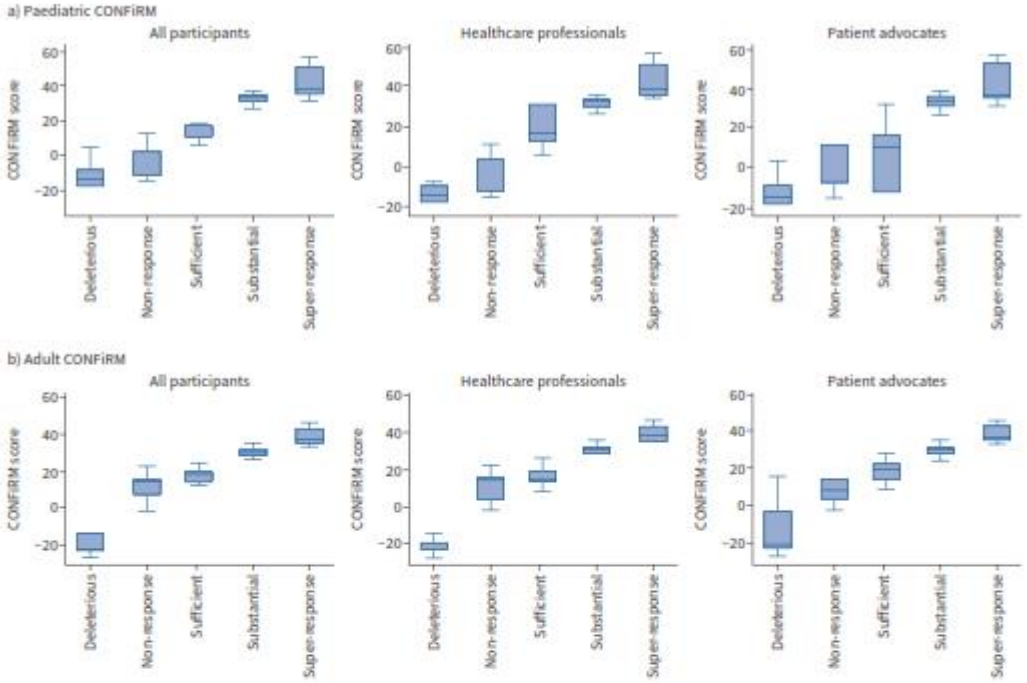

FIGURE 4 CompOsite iNdex For Response in asthMa (CONFiRM) score in step 3 (internal validation). a) Paediatric CONFiRM. b) Adult CONFiRM. Magnitude of response was most frequently selected (modal) by healthcare professionals and patient advocates for 50 patient profiles. Definitions of overall magnitude of response used in the study are presented in box 1. Total score for these patient profiles was calculated based on weights for each outcome measure assigned in step 2. The analysis was weighted by case frequency. The CONFiRM score for each patient case is 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–Wallis χ^2=2623.1, p<0.0001; χ^2=2506.5, p<0.0001; χ^2=2657.1, p<0.0001 for all participants, patient advocates and healthcare professionals, respectively) and adult CONFiRMs (χ^2=2974.7, p<0.0001; χ^2=2854.3, p<0.0001; χ^2=3216.3, p<0.0001).

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 because 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 patients with severe asthma on biologicals and the lived experience of participants who are taking or have previously taken biologicals. Patient profiles were developed from large observational studies with different biologicals 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 that 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

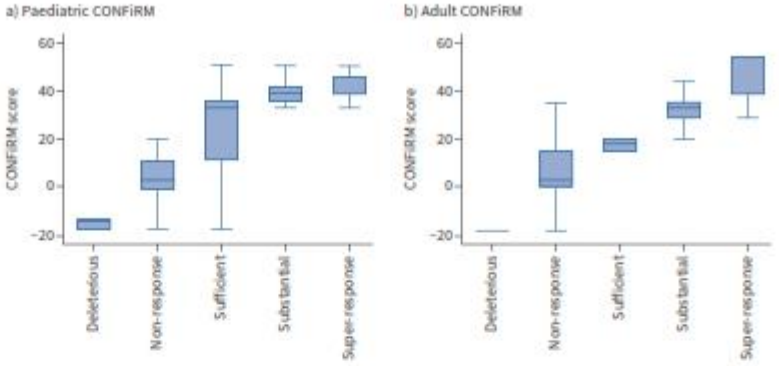

FIGURE 5 CompOsite iNdex For Response in asthMa (CONFiRM) score in step 4 (external validation). a) Paediatric CONFiRM. b) Adult CONFiRM. Magnitude of response was most frequently selected (modal) by healthcare professionals for 15 patient profiles. Definitions of magnitude of response used in the study are presented in box 1. Total score for these patient profiles was calculated based on relative weights for each outcome measure assigned at step 2. The Analysis was weighted by case frequency. The CONFiRM score for each patient case is 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–Wallis χ^2=502.7, p<0.0001) and adult CONFiRMs (χ^2=648.5, p<0.0001). Similar results were found for adult patient profiles where maintenance oral corticosteroid was not used at baseline (supplementary figure S11).

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

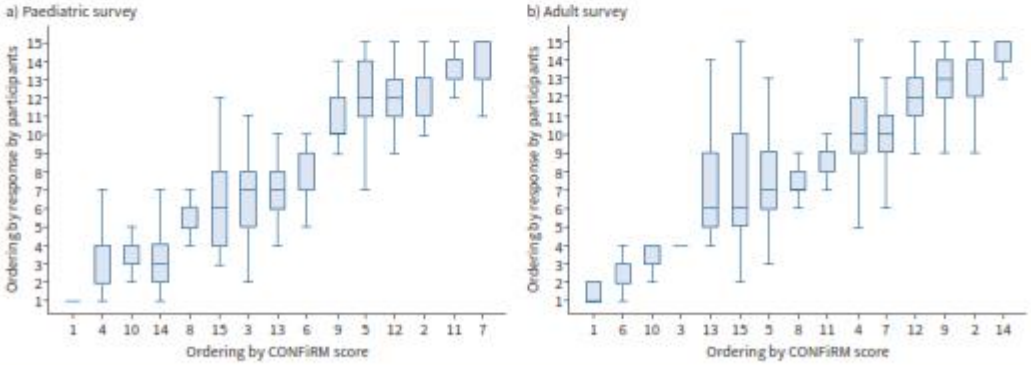

FIGURE 6 Ranking of the 15 patient profiles in order of improvement on biologics from 1st (worsening) to 15th (largest improvement) in stage 4. a) Paediatric patient profiles. b) Adult patient profiles. Ranks for each patient profile are represented by box and whisker plots (box: median with 25th and 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 CompOsite iNdex For Response in asthMa (CONFiRM) tools demonstrated excellent external validity (Spearman correlation coefficients r=0.9 and 0.8 for paediatric and adult patient profiles, respectively (p<0.0001)).

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biologicals or maintenance OCS. 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. ICCs 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 biological 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, maintenance OCS, 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 because not all patients with severe asthma respond to high-cost biologicals. The overall magnitude of response definitions with their corresponding scores should assist HCPs in assessing whether a biological has provided a substantial benefit to patients. Our data provide preliminary score ranges for different magnitudes of response. This should inform a shared decision with the patient to continue a biological or pursue an alternative approach. Further studies should confirm the appropriate time for assessing response, confirm 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. 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 biologicals 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 biologicals for severe asthma. In conclusion, the development of the patient-centred CONFiRM scores to quantify response to biologicals 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.

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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	Total n (%)	PA n (%)	HCP n (%)	Adult COMSA	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

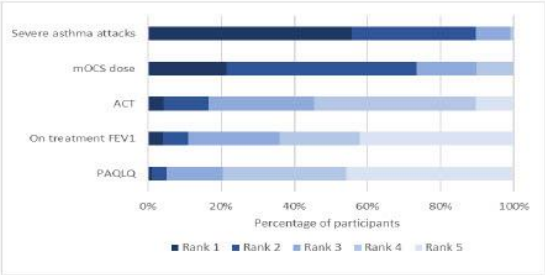
	Adult profiles n (%) n=42	Paediatric profiles n (%) n=46
Duration of treating patients with severe asthma		
0-5 years	1 (2.4)	3 (6.5)
5-10 years	5 (11.9)	2 (4.3)
10-20 years	16 (38.1)	18 (39.1)
Over 20 years	20 (47.6)	23 (50.0)

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)

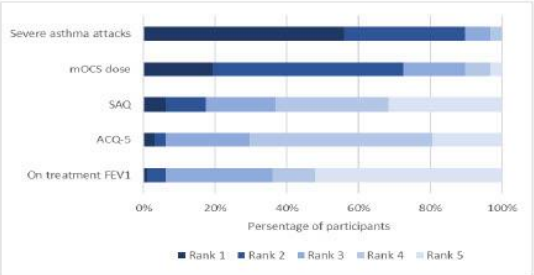
Figures represent number (percentage) of participants.* Others: Czech Republic (n=3); Finland (n=3); Poland (n=3); Spain (n=3); Switzerland (n=3); United States (n=3); China (n=2); Denmark (n=2); Turkey (n=2); Estonia (n=1); Greece (n=1); Japan (n=1); Norway (n=1); Romania (n=1); Singapore (n=1); Slovenia (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[0]: 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[0]: 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)

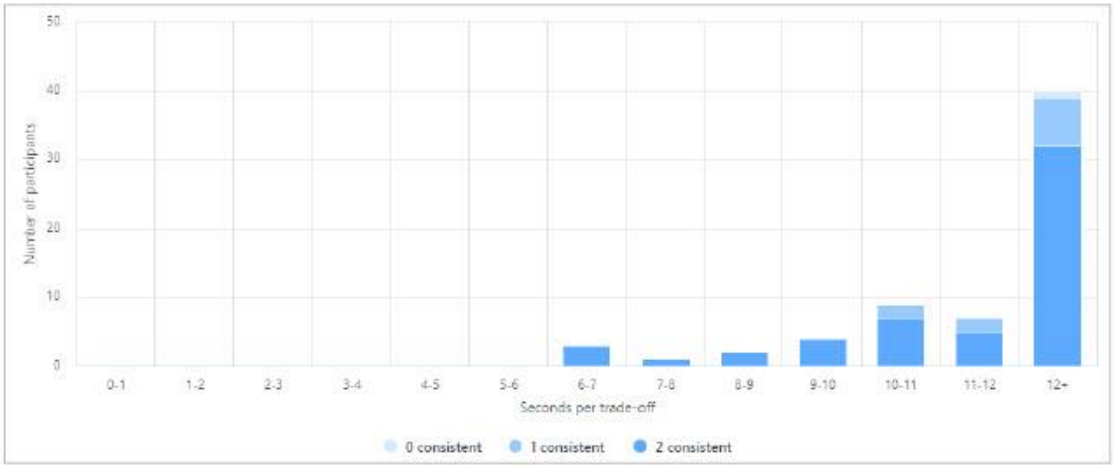
B. Adult CONFiRM

	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)

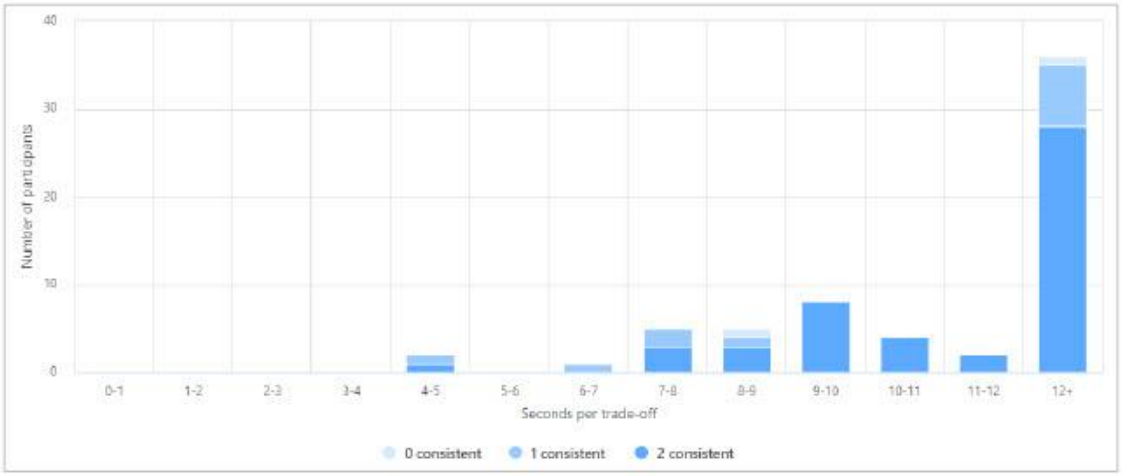
Figures are means (standard deviations) maximal preference weight from 1000Mind software from step 2. The consistency of each participant's choices was tested by repeating two previously answered scenarios. Consistent is defined by reporting the same response (patient 1 over patient 2 or 'they are the 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

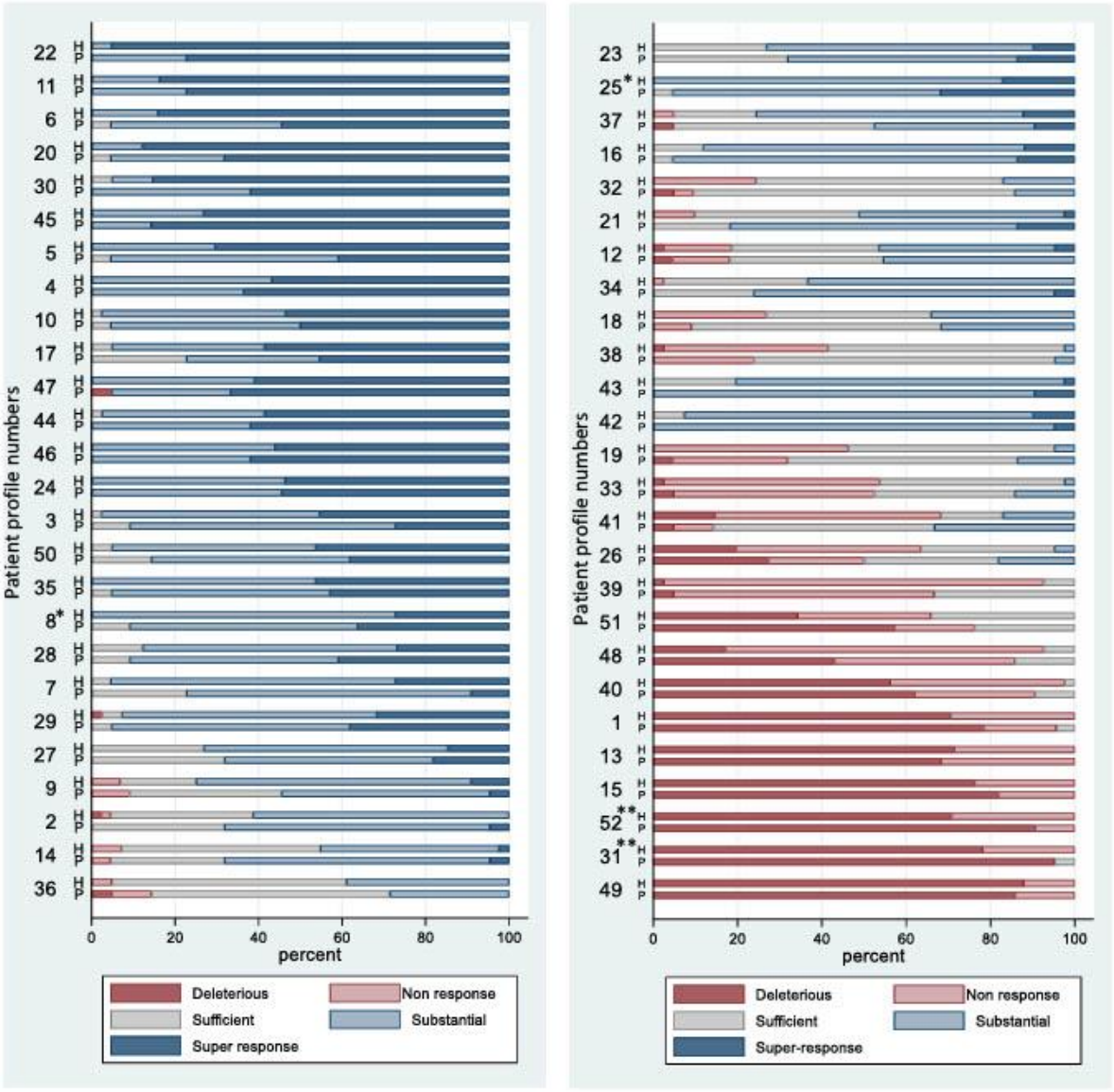
	All participants, mean weights %			Restricted to participants who consistently answered repeated scenarios, mean weights %		
	Does this order seem about right to you?		Total (n=66)	Does this order seem about right to you?		Total (n=54)
	Yes (n=47)	No (n=19)		Yes (n=38)	No (n=16)	
Severe asthma attacks:[5,24] 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

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)

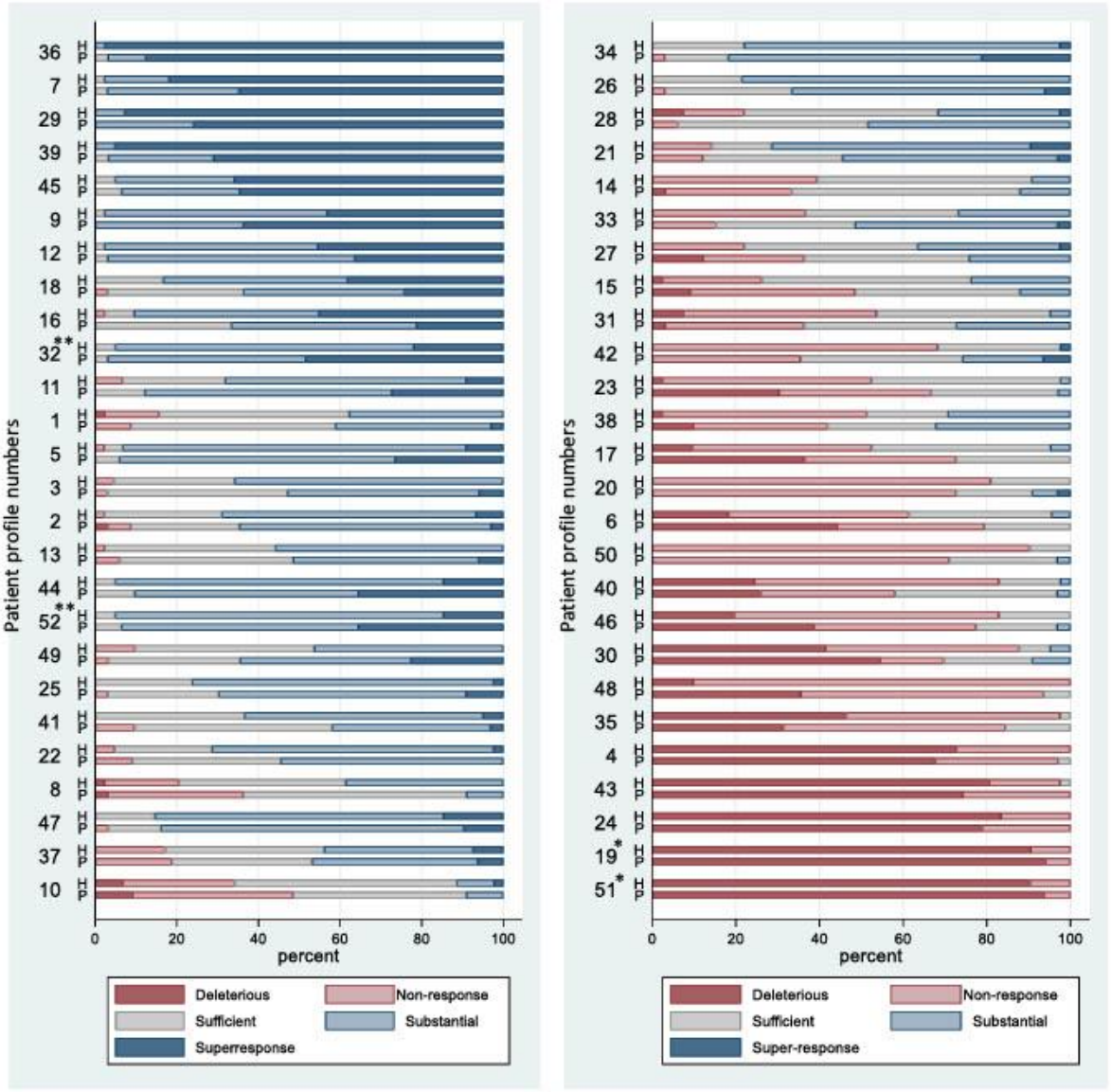
Figures represent number (percentage) of participants.*Other countries: Australia (n=3); Switzerland (n=3), China (n=2), Czech Republic (n=2), Finland (n=2), Poland (n=2), Romania (n=2), Turkey (n=2), Austria (n=1), Bulgaria (n=1), Croatia (n=1), Estonia (n=2), Japan (n=1), South Korea(n=1), Singapore(n=1), 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.

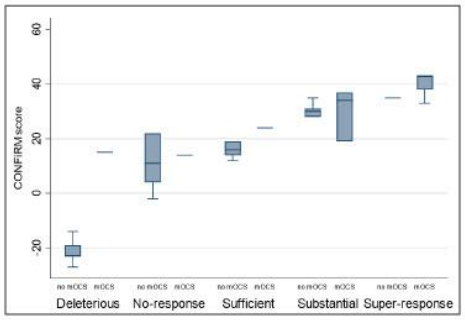
Table S15. Median CONFiRM scores for each overall magnitude of response (step 3)

	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)

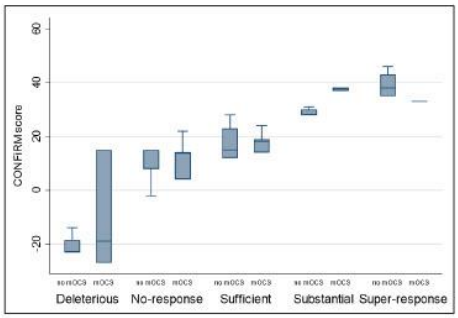
CONFiRM, CompOsite iNdex For Response in asthMa; HCPs, healthcare professionals.

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

A. Paediatric CONFiRM



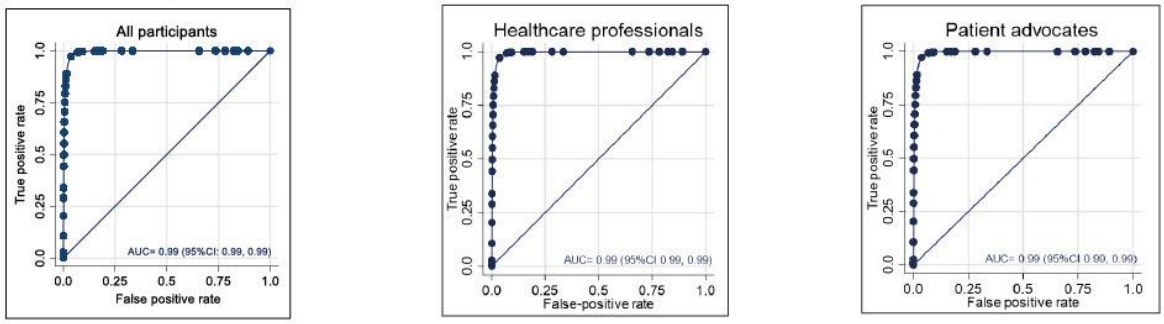
B. Adult CONFiRM Response



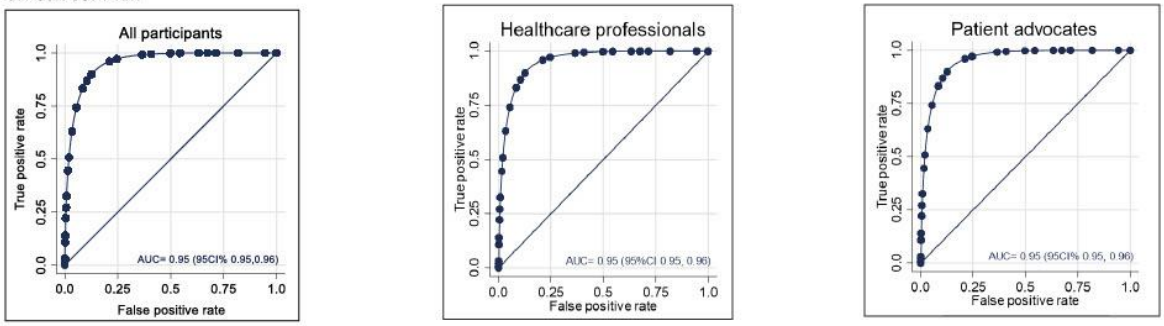
Box and whisker plot show the 1000minds score for patient profile with each magnitude of overall response by OCS treatment at baseline. Response (deleterious to super-response) was the most frequent (modal) response by all participants for each of the 50 patient profiles. Total composite score for these 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



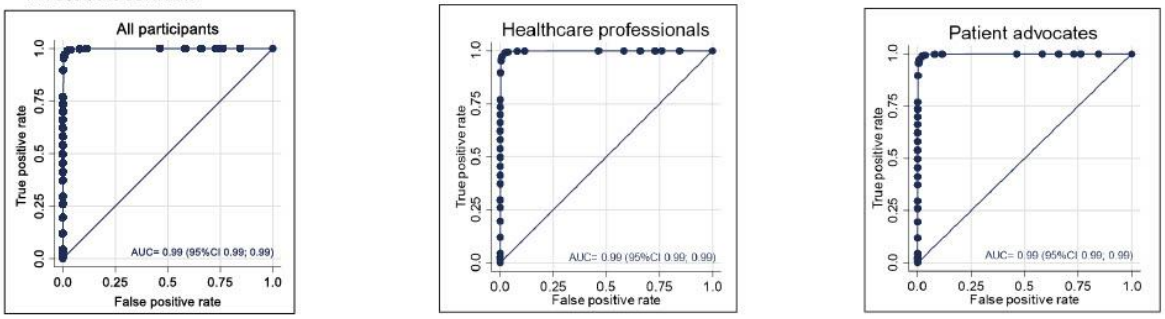
B. Adult CONFiRM



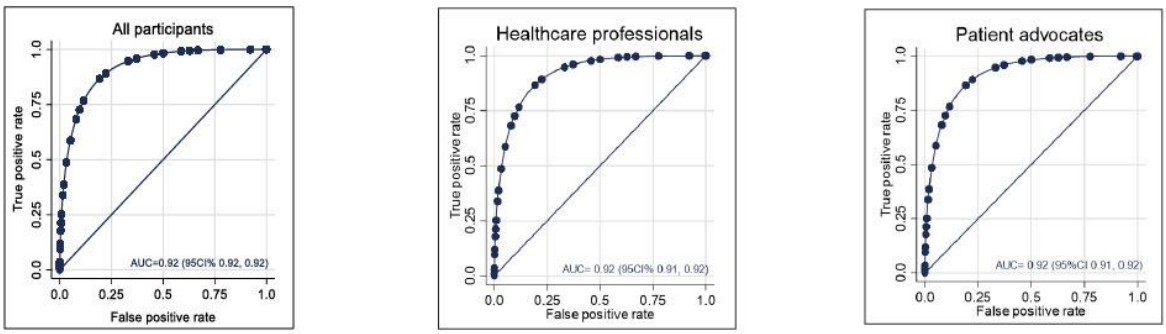
Gold standard taken from participants' rating of response for 50 patient profiles. Compared to CONFiRM score for each patient case. Substantial response is "an improvement in asthma that a patient would consider as being 'big enough' to justify the use of biological therapy for their asthma (Box 1). 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



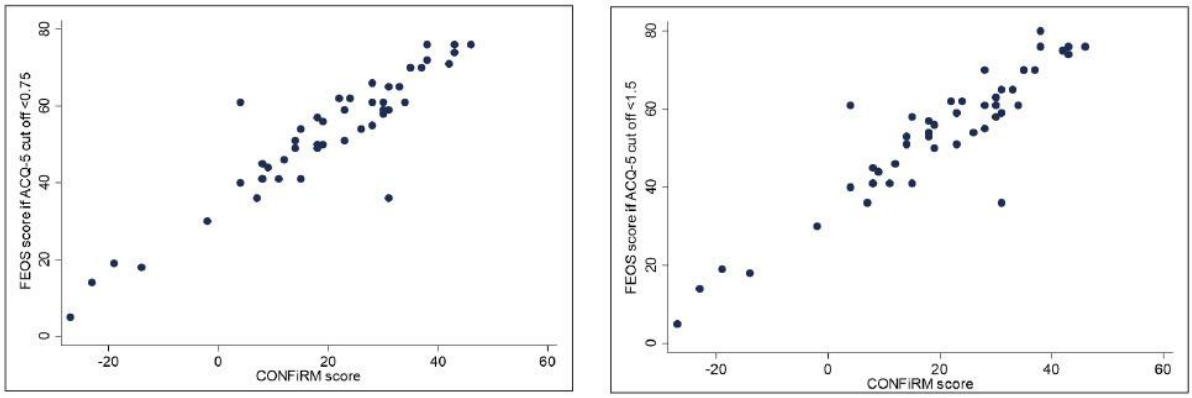
Gold standard taken from participants' rating of response for 50 patient profiles. Compared to CONFiRM score for each patient case. Sufficient response is "the smallest improvement in asthma that a patient would consider as important and would help in further doctor-patient decision-making (Box 1)". 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

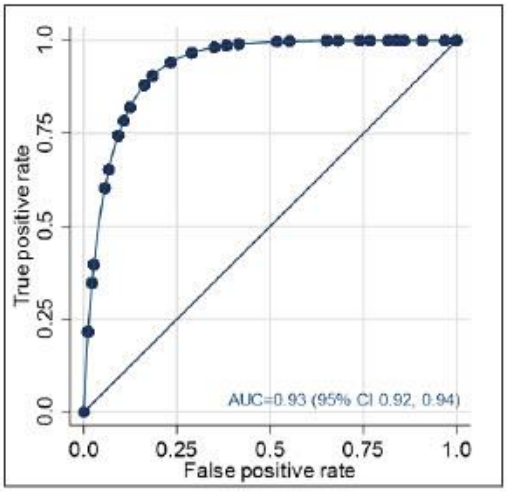
AUC, area ander the curve; CONFiRM, CompOsite iNdex For Response in asthMa; HCPs, healthcare professionals; NA, not avaliable because AUC not calcuable as data either perfectly predicts outcome or zero participants in one cell; mOCS, maintenance oral corticosteroids.

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)

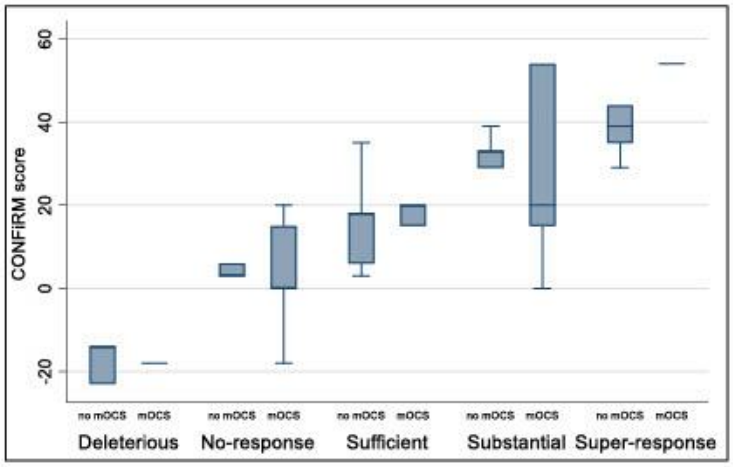
Intraclass correlation coefficient[14] (ICC) estimates and their 95% confident intervals were calculated using STATA software version 16.1 based on an absolute-agreement, 2-way mixed-effects model. ICC was used to calculate agreement between responses from HCP for the repeated patient profiles. Values 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.

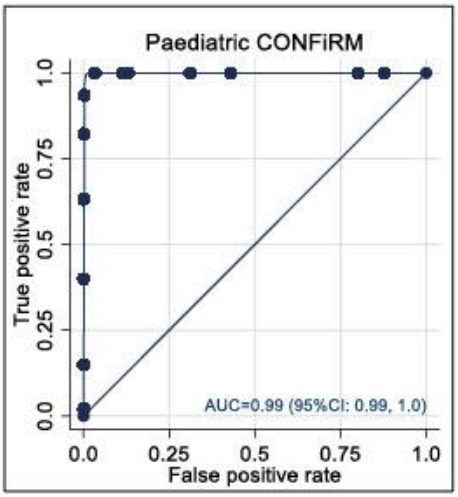
Figure S9. Sensitivity analysis for adult patient profiles depending on taking maintenance oral corticosteroids at baseline (step 4)

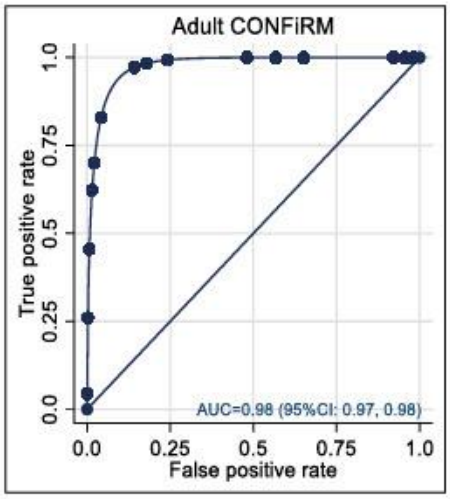


Box and whisker plot show the 1000minds score for patient profile with each magnitude of overall response by OCS treatment at baseline. Response (deleterious to super-response) was the most frequent (modal) response by all participants for each of the 15 patient profiles in the step 4. Total composite 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.

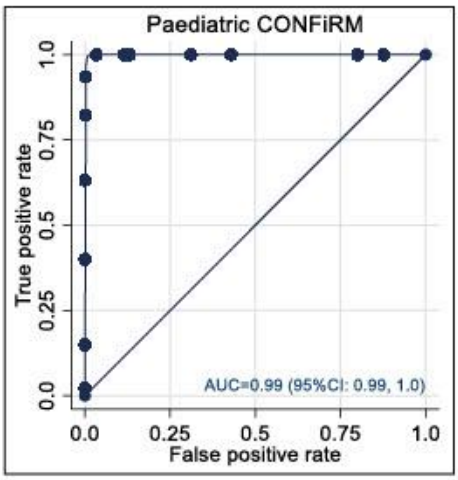
Figure S10. Receiver operator curves (ROC) for substantial and sufficient responses. (step 4)

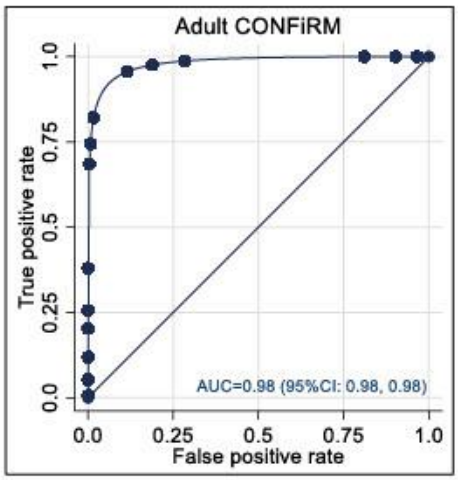
A. ROC for substantial response compared with less than substantial response.





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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