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].

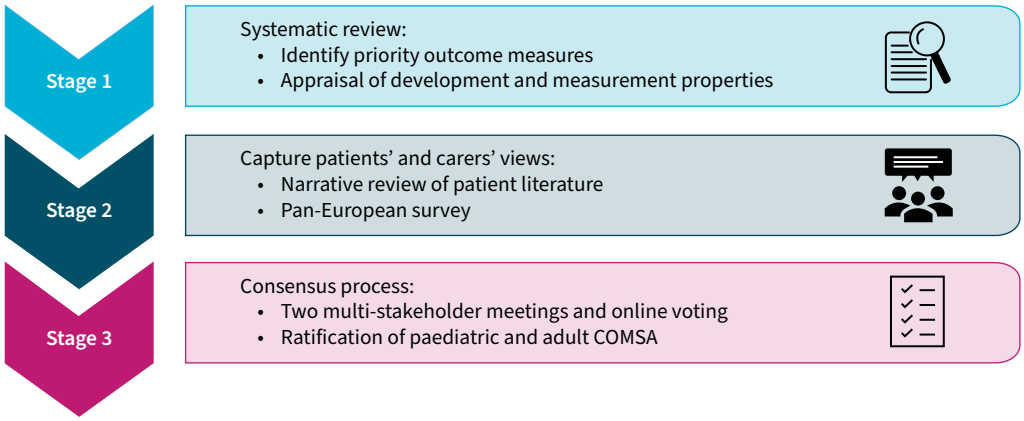

FIGURE 1 Core Outcome Measures set development process. COMSA: Core Outcome Measures for paediatric and adult Severe Asthma.

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 $\geqslant$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

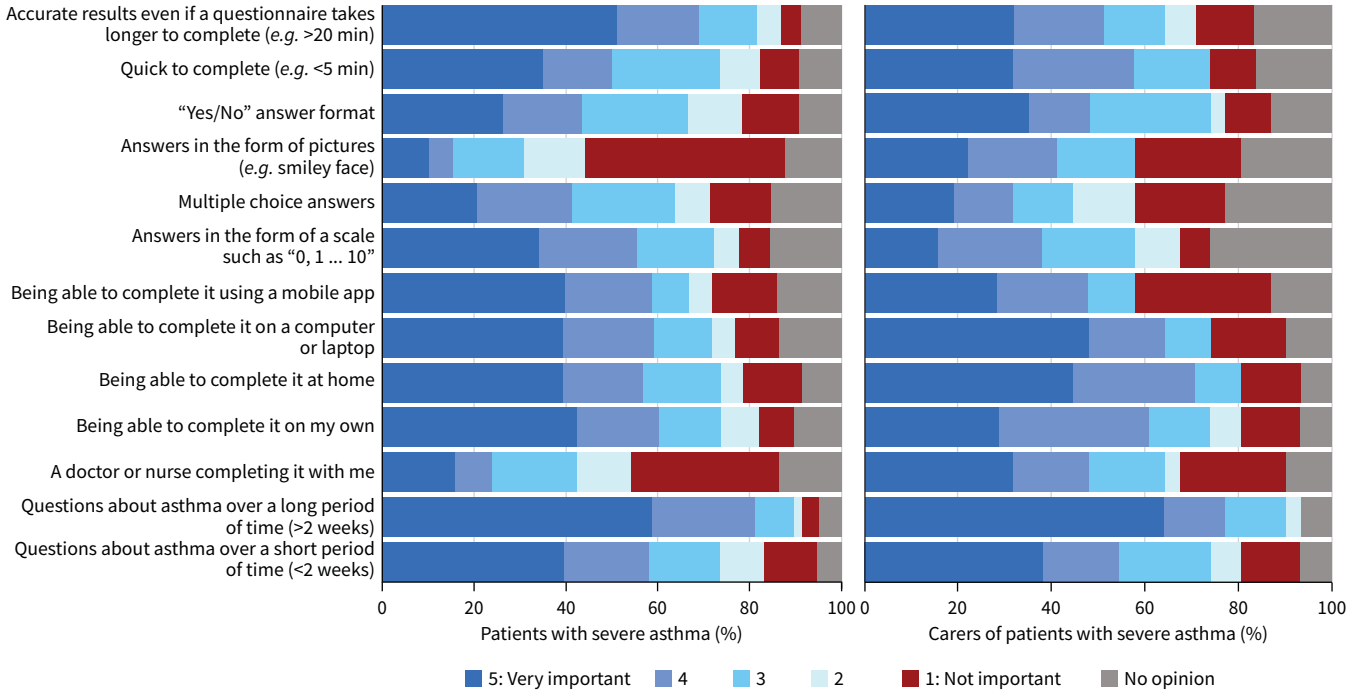

FIGURE 2 Patients' and carers' views about characteristics of questionnaires for assessment of severe asthma according to the pan-European survey.

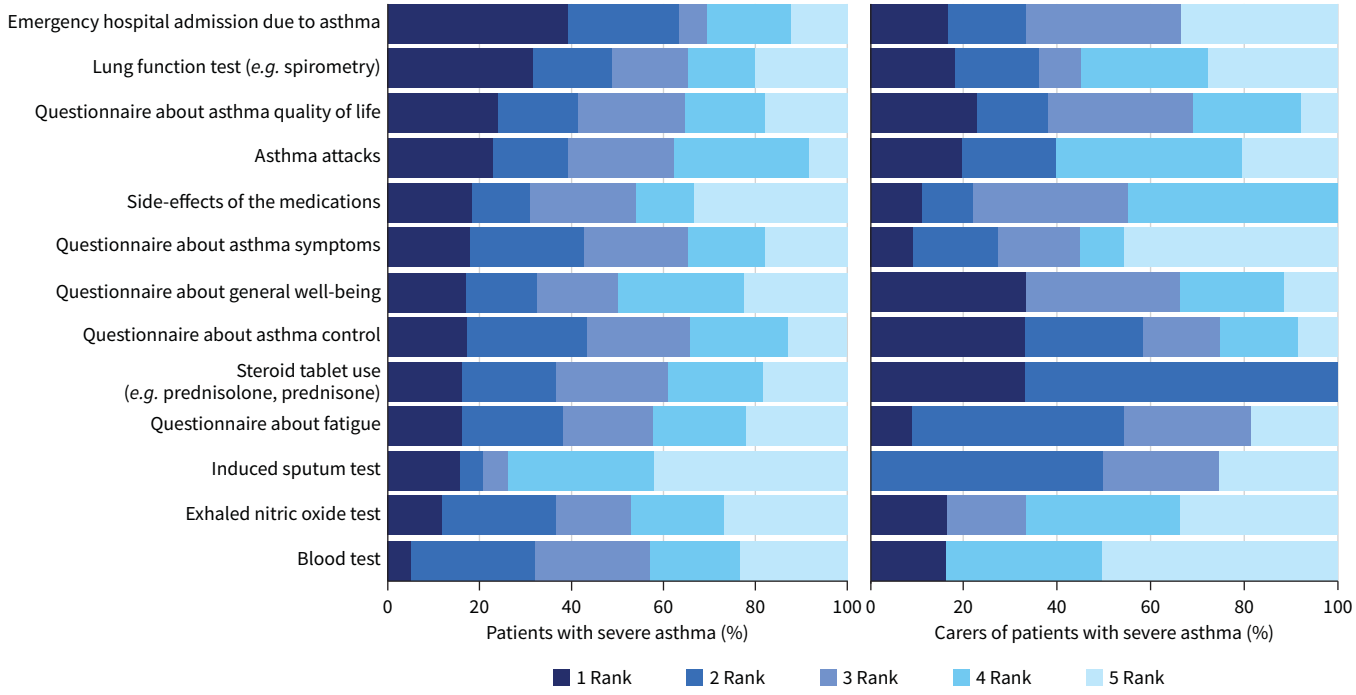

FIGURE 3 Overall views of patients and carers about outcome measures for assessment of severe asthma according to the pan-European survey. Respondents were asked to select five outcome measures and rank their importance from 1=most important to 5=least important, for use in future severe asthma trials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

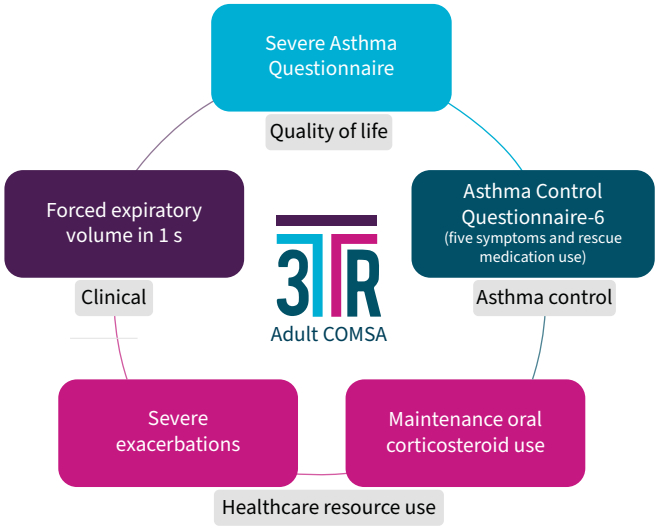

FIGURE 4 The adult Core Outcome Measures set for severe asthma clinical trials. Forced expiratory volume in 1 s should be reported as z-scores using the Global Lung Function Initiative predictive equations [58], annual severe exacerbations as per the European Respiratory Society/American Thoracic Society 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

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.

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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.

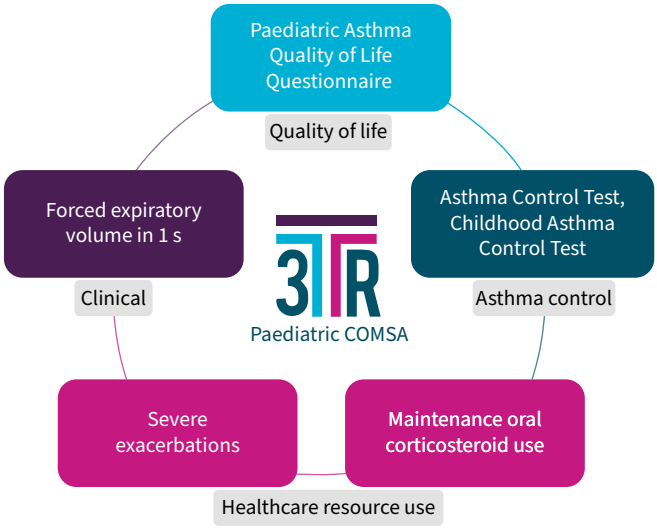

FIGURE 5 The paediatric Core Outcome Measures set for severe asthma clinical trials. Forced expiratory volume in 1 s should be reported as z-scores using the Global Lung Function Initiative predictive equations [58], annual severe exacerbations as per the European Respiratory Society/American Thoracic 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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