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Identifying and appraising outcome measures for severe asthma: a systematic review

Anna Rattu, Ekaterina Khaleva, Chris Brightling, Sven-Erik Dahlén, Apostolos Bossios, Louise Fleming, Kian Fan Chung, Erik Melén, Ratko Djukanovic, Rekha Chaudhuri, Andrew Exley, Gerard H. Koppelman, Arnaud Bourdin, Franca Rusconi, Celeste Porsbjerg, Courtney Coleman, Clare Williams, Hanna Nielsen, Elizabeth Davin, Phil Taverner, Sofia Romagosa Vilarnau, Graham Roberts, on behalf of the 3TR consortium Respiratory Work Package

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ABSTRACT

Background: Valid outcome measures are imperative to evaluate treatment response, yet the suitability of existing endpoints for severe asthma is unclear. This review aimed to identify outcome measures for severe asthma and appraise the quality of their measurement properties.

Methods: A literature search was performed to identify 'candidate' outcome measures published between 2018 – 2020 (PROSPERO, CRD42020204437). A modified Delphi exercise was conducted to select 'key' outcome measures within healthcare professional, patient, pharmaceutical, and regulatory stakeholder groups. Initial validation studies for 'key' measures were rated against modified quality criteria from COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN). The evidence was discussed at multi-stakeholder meetings to ratify 'priority' outcome measures. Subsequently, four bibliographic databases were searched from inception to identify development and validation studies for these endpoints. Two reviewers screened records, extracted data, assessed their methodological quality, and graded the evidence according to COSMIN.

Results: 96 outcome measures were identified as 'candidates', 55 as 'key', and 24 as 'priority' for severe asthma; including clinical, healthcare utilisation, quality of life, asthma control, and composite. 32 studies reported measurement properties of 17 'priority' endpoints from the latter three domains. Only SAQ and C-ACT were developed with input from severe asthma patients. The certainty of evidence was 'low' to 'very low' for most 'priority' endpoints across all measurement properties, and none fulfilled all quality standards.

Conclusion: Only two outcome measures had robust developmental data for severe asthma. This review informed development of core outcome measures sets for severe asthma.

Keywords: COSMIN, measurement properties, outcome measures, validity, severe asthma, systematic review

Take home message: This study identified and appraised the validity of selected outcome measures for severe asthma with input from key stakeholders. Only the Severe Asthma Questionnaire and Childhood Asthma Control Test had robust developmental data for severe asthma.

Abbreviations: ATS / ERS (American Thoracic Society / European Respiratory Society), AQLQ (Asthma Quality Of Life Questionnaire), AQLQ-S (Asthma Quality Of Life Questionnaire Standardised), Mini-AQLQ (Mini Asthma Quality Of Life Questionnaire), ACT (Asthma Control Test), ACQ (Asthma Control Questionnaire), ACCI (Asthma Control and Communication Instrument), C-ACT (Childhood Asthma Control Test), CASI (Composite Asthma Severity Index), COSMIN (COnsensus-based Standards for the selection of health Measurement Instruments), FDA (Food and Drug Administration), FEV₁ (forced expiratory volume), FeNO (fractional exhaled nitric oxide), GRADE (Grading of Recommendations Assessment, Development and Evaluation), HRU (Healthcare resource utilisation), MCID (Minimal Clinical Important Difference), Mini-PAQLQ (Mini Paediatric Asthma Quality Of Life Questionnaire), mOCS (maintenance oral corticosteroids), OCS (Oral corticosteroids), PAQLQ (Paediatric Asthma Quality Of Life Questionnaire), PAQLQ-S (Paediatric Asthma Quality Of Life Questionnaire Standardised), PROM (Patient-reported Outcome Measures), QoL (Quality of Life), RoB (Risk of Bias), SAQ (Severe Asthma Questionnaire), St George's Respiratory Questionnaire (SGRQ).

1 BACKGROUND

Asthma is the most prevalent chronic respiratory condition affecting an estimated 339 million people worldwide¹⁻³. Approximately 5-10% of these patients have severe asthma^{2,4}. The American Thoracic Society / European Respiratory Society (ATS/ERS), define severe asthma as requiring treatment with high-dose inhaled corticosteroids plus additional controller medication(s) or oral corticosteroids (OCS) to maintain disease control, or which remains sub-optimally controlled despite adherence once differential diagnoses have been addressed and any co-morbidities treated². The impaired quality of life (QoL), adverse effects of long term OCS use, and disproportionately high healthcare cost are causes of concern in this group of patients⁵⁻¹⁰.

A more nuanced understanding of the pathophysiological mechanisms underlying severe asthma has facilitated the emergence of new-generation treatments, including ‘biologics’, which can reduce exacerbation rates¹¹, OCS use¹², and improve lung function¹³. In studies investigating these interventions the selection of efficacy endpoints is influenced by multiple aspects of trial design and analysis. However, it is imperative that the outcome measures have robust measurement properties to ensure good quality and appropriate interpretation of results. The selection of outcome measures should be grounded in whether they are valid, reliable, and responsive and sensitive to changes when evaluating differences in the treatment groups¹⁴.

The National Institutes of Health (NIH) recommendations¹⁵⁻²⁰ for outcome measurement instruments for asthma are the status quo for clinical practice and research, yet there is no consensus on which outcome measures are important to patients with severe asthma and have robust psychometric properties in this population. Further, guidelines recommend the implementation of patient-reported outcome measures (PROMs) capturing domains such as QoL and asthma control to evaluate treatment response, but do not propose specific instruments²¹. On the other hand, outcomes that patients consider a treatment priority, such as QoL^{8,22}, are not consistently reflected in physicians’ approach to evaluating treatment response²³. It is particularly important to use patient-centred outcome measures in effectiveness studies of biologics to justify the high economic²⁴ and individual-level treatment burden^{6,8,25}. A comprehensive view of the validity of outcome measures for severe asthma would also enable the selection of the most appropriate instruments for better disease management by patients and healthcare professionals in practice.

This systematic review aimed to (i) identify patient-centred outcome measures considered to be a ‘priority’ for severe asthma by relevant stakeholders (patient representatives, which included patients, parents/carers, and patient advocacy organisations; healthcare professionals, pharmaceutical, and regulatory representatives) and, (ii) critically appraise, compare, and qualitatively summarize the quality of studies reporting the development and measurement properties of each ‘priority’ outcome measure using the CONsensus-based Standards for the selection of health Measurement INSTRUMENTS (COSMIN) guidelines^{26,27}.

2 METHODS

This systematic review is registered with the International Prospective Register of Systematic Reviews (PROSPERO registration: CRD42020204437). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist has been used to guide the reporting of this systematic review²⁸ (Appendix D.1). The methods are described in Figure 1 and full details are reported in the online supplement (Appendix A and B).

2.1 Steps 1 – 3: Identifying ‘priority’ outcome measures for severe asthma

In Step 1, a literature search was performed to identify ‘candidate’ outcome measures (patient-reported, clinical, composite, and imaging) published in four bibliographic databases between May 7, 2018 – May 7, 2020. Subsequently, a modified Delphi exercise was conducted within four stakeholder groups recruited from across Europe (**Step 2**). This involved two consecutive rounds of surveys wherein stakeholders ranked the importance of ‘candidate’ outcome measures on a 9-point Likert scale (based on Grading of Recommendations Assessment, Development and Evaluation (GRADE)²⁹). ‘Candidate’ outcome measures which $\geq 50\%$ participants in each stakeholder group rated as critical (7-9 on 9-point Likert scale) were ratified as ‘key’ outcome measures; measures for which consensus was not achieved were discussed at a multi-stakeholder web-conference to obtain agreement on whether they should be classified as ‘key’. Emphasis was placed on collating views about ‘candidate’ outcome measures ranked as ‘critical’ and ‘important’ by patient representatives in the round two survey.

Step 3 involved a literature search to identify initial validation studies for selected ‘key’ outcome measures, followed by appraisal of the quality of measurement property results against modified COSMIN quality criteria. The evidence was discussed at two multi-stakeholder meetings together with supporting patient-voice evidence³⁰, followed by online voting to select ‘priority’ outcome measures for adult and paediatric severe asthma. For this voting process data were grouped by patient representatives, and ‘academic’ representatives inclusive of healthcare professionals, pharmaceutical, and regulatory representatives. Outcome measures which $\geq 33\%$ participants in at least one of two stakeholder groups voted as a ‘priority’ were included.

2.2 Step 4: Development and measurement properties of ‘priority’ outcome measures

2.2.1 Search strategy

A search strategy was developed on EMBASE (OVID) and subsequently adapted for the following databases: MEDLINE (OVID), CINAHL (EBSCOhost, Cumulative Index to Nursing and Allied Health Literature), and ISI Web of Science (Thomson Web of Knowledge) (Appendix B.2). Databases were searched from the inception to 20 July 2020. The citation lists of identified studies and reference lists of systematic reviews were searched for additional articles.

2.2.2 Eligibility criteria

The inclusion criteria to identify eligible studies were as follows:

Population: adults (≥ 18 years) and/or children and adolescents (6-17 years) with a diagnosis of asthma. We collated data for all severities of asthma and accounted for the differing relevance for severe asthma in the modified GRADE assessment.

Intervention: any asthma therapy or no intervention.

Comparator: any comparator group including placebo or no comparator.

Study outcomes: outcome measures considered a 'priority' by key stakeholders (Appendix A.4). For patient-reported and composite outcome measures, studies were also eligible if they validated the 'priority' outcome measure with minor modifications according to cultural setting e.g. changing the list of activities to includes items that are more suited to tropical/cold climate.

Study designs: studies aiming to develop ('development' or 'inauguration' article), investigate the content validity (extent to which the outcome measure assesses the concept of interest) and/or one or more measurement properties of a 'priority' outcome measure (including studies with age and sociodemographic subgroups, and different modes of administration).

The exclusion criteria were as follows: systematic reviews and meta-analyses, narrative reviews, discussion papers, commentaries, non-research letters and editorials, abstracts only (e.g. conference paper), animal studies, non-asthma studies e.g. viral bronchiolitis, viral associated wheeze. Studies which reported on linguistic validity, translated, or modified versions of 'priority' patient-reported and composite outcome measures, or used 'priority' measures as outcome measurement instruments, such as clinical trials, were also excluded. Studies reporting correlations between a 'priority' clinical outcome measure and guidelines as 'gold standard' were excluded as they are susceptible to publication bias.

2.2.3 Study selection and data extraction

References were pooled and de-duplicated in Endnote version X9 (Thomson Reuters, Philadelphia, PA), and subsequently uploaded to Rayyan31 (rayyan.qcri.org). Study titles, abstracts, and full-text articles were screened independently by two reviewers (AR, EK) according to the predefined selection criteria. Data extraction from included articles was performed into a pilot-tested form based on the COSMIN guidelines^{26,27} by one reviewer (AR), and cross-checked by the second reviewer (EK). Any disagreements were resolved through discussion, and, if necessary, involvement of the third reviewer (GR).

2.2.4 Quality appraisal strategy

The methodological quality and certainty of evidence was evaluated in a three-step process by two independent reviewers (AR, EK). Any discrepancies were resolved through discussion, or arbitration by the third reviewer (GR). First, the Risk of Bias (RoB) of developmental, content validation, and studies reporting other measurement properties was assessed using the COSMIN checklist for PROMs^{26,32}. For non-patient reported outcomes (including

composites with clinician-performed components), a separate checklist³³ was used. The definitions of measurement properties are provided in Table S1. Second, results of the measurement properties from each study were rated against quality criteria (Table S2) and qualitatively pooled to generate an overall rating of sufficient (+), insufficient (-), or indeterminate (?). Third, the certainty of evidence was determined using a modified GRADE approach^{26,32,34}. The results were summarized using narrative synthesis.

3 RESULTS

3.1 Steps 1-3: Identifying ‘priority’ outcome measures for severe asthma

The detailed results for identifying ‘priority’ outcome measures for severe asthma can be found in Appendix C. Briefly, a total of 96 ‘candidate’ outcome measures were retrieved from the literature search. 55 ‘key’ outcome measures were selected following the modified Delphi exercise. Validation data were available for 32 ‘key’ patient-reported and composite outcome measures, and one healthcare resource utilisation (HRU) measure, while no data were identified for clinical outcome measures. The ‘priority’ outcome measures selected following the multi-stakeholder meetings and online voting are presented in Figure 2.

3.2 Step 4: Appraisal of development and measurement properties of ‘priority’ outcome measures

3.2.1 Study characteristics

A total of 32 studies were included; 16 met the inclusion criteria for the adult population, 12 studies for the paediatric population, while 4 were eligible for both populations (Figure 3). The characteristics of included studies are presented in Tables S3 and S4 for adult and paediatric populations respectively. 12 and seven articles described the development and/or measurement properties of QoL measures for adults³⁵⁻⁴⁶, and children and adolescents⁴⁷⁻⁵³, respectively. Only one content validation study was identified⁵⁴. Six articles reported the development and/or measurement properties of asthma control instruments for adults⁵⁵⁻⁶⁰, while eight articles were included for the paediatric population^{55,56,58,60-64}. One study validated the Asthma Control and Communication Instrument (ACCI), a composite tool prioritised for adults⁶⁵, and one reported the Composite Asthma Severity Index (CASI), a tool for patients older than 6 years⁶⁶. Of the included studies, ten involved participants with severe asthma; but in most cases the percentage of this population was <50%, and differing definitions of asthma were used (including guidelines, physician diagnosis, and self-report).

3.2.2 Risk of bias and quality of evidence for ‘priority’ outcome measures

The developmental process for the ‘priority’ outcome measures can be found in Table S5-S6. The characteristics of the ‘priority’ QoL, asthma control, and composite outcome measures are presented in Table 1. An overview of the rating of measurement property results against COSMIN quality criteria, and the quality of evidence per ‘priority’ outcome measure for adult

and paediatric severe asthma is presented in Table 2. Structural validity (for asthma control measures based on a reflective model) and measurement error were not assessed in any of the identified studies. The most common reason for downgrading was indirectness, as <50% of participants in multiple studies had severe asthma.

According to the COSMIN RoB checklist, the assessments for studies ranged from ‘inadequate’ to ‘very good’ (Tables S7 and S8). For ‘doubtful’ or ‘inadequate’ ratings, frequent methodological limitations included lack of description of subgroup characteristics for test-retest reliability; small sample size; inappropriate statistical methods for evaluating responsiveness (or reporting of responsiveness index only), and lack of information on unidimensionality when assessing internal consistency.

3.2.2.1 ‘Priority’ quality of life outcome measures for adult severe asthma

Content validity was rated most favourably for the Severe Asthma Questionnaire (SAQ) with sufficient ‘moderate’ quality evidence across all domains. The SAQ was the only ‘priority’ measure developed with input from adults with severe asthma. The Asthma Quality of Life Questionnaire (AQLQ) and its ad hoc standardised and mini versions had variable ratings with ‘low’ to ‘very low’ quality evidence.

For internal consistency there was sufficient ‘very low’ to ‘moderate’ quality evidence for the AQLQ, the Asthma Quality of Life Questionnaire Standardised (AQLQ-S) and Mini-AQLQ. Likewise, all measures had good to excellent test-retest reliability, but the quality of evidence was variable, with only the SAQ scored as ‘moderate’ quality evidence. The Mini-AQLQ showed strong correlation with AQLQ scores, indicating sufficient criterion validity. Only the Mini-AQLQ and SAQ had sufficient evidence for construct validity – scores on both instruments had strong correlations with comparator QoL measures, and weak correlations with FEV1% predicted. The AQLQ and AQLQ-S had sufficient, but ‘low’ and ‘very low’ quality evidence for responsiveness to change; the change scores for patients who were unstable between study visits exceeded the Minimal Clinical Important Difference (MCID).

3.2.2.2 ‘Priority’ asthma control outcome measures for adult severe asthma

The Asthma Control Test (ACT), Asthma Control Questionnaire 5 (ACQ-5), and ACQ-6 had insufficient to inconsistent evidence for content validity. The quality of evidence was ‘very low’ primarily because no patients were involved in the developmental process. However, all the questionnaires had good to excellent internal consistency and test-retest reliability to support the sufficient ratings. The shortened ACQ-6 and ACQ-5 showed strong correlations with the original ACQ-760, illustrating sufficient criterion validity. In contrast, there was insufficient ‘low’ to ‘very low’ quality evidence for construct validity and responsiveness to change for all asthma control instruments. There were studies reporting moderate correlations between scores on ‘priority’ instruments and comparators such as physician assessed asthma control and QoL, and weak correlations with FEV1. Similarly, some studies reported that patients with unstable asthma had meaningful changes in priority control instrument scores i.e. changes exceeding MCID. However, after qualitatively pooling the evidence the a priori threshold for hypotheses was not fulfilled for either of the measurement properties.

3.2.2.3 ‘Priority’ composite outcome measures for adult severe asthma

The ACCI was awarded sufficient ratings for relevance and comprehensibility, as patients were involved in its development, but comprehensiveness was rated insufficient. Of the other measurement properties appraised, there was only sufficient, albeit ‘low’ quality evidence, for construct validity. ACCI scores had moderate to strong correlations with asthma control and asthma-specific QoL, and relatively weaker correlations with generic QoL.

3.2.2.4 ‘Priority’ quality of life outcome measures for paediatric severe asthma

Content validity was rated inconsistent for all ‘priority’ QoL instruments except the Paediatric Asthma Quality of Life Questionnaire (PAQLQ), which had sufficient evidence for comprehensibility. The quality of evidence was ‘very low’ to ‘low’ as only patients with mild-to-moderate asthma were involved in the development. There was sufficient evidence for other measurement properties appraised, except Mini-PAQLQ, which was rated insufficient for internal consistency. The quality of evidence was predominantly higher for the PAQLQ and Mini-PAQLQ compared to the PAQLQ-S.

3.2.2.5 ‘Priority’ asthma control outcome measures for paediatric severe asthma

The Childhood Asthma Control Test (C-ACT) had the most robust developmental process; there was sufficient ‘moderate’ quality evidence for relevance and comprehensibility, with 28% of the patients in the developmental study diagnosed with severe asthma. The ACT, ACQ-5, ACQ-6, and ACQ-7 received inconsistent and insufficient ratings for relevance and comprehensiveness respectively. However, the ACQ versions performed better than ACT in comprehensibility as children and adolescents were consulted about the phrasing of items and response options. The ‘priority’ asthma control measures were rated sufficient for all measurement properties assessed, except ACT which had insufficient evidence for responsiveness to change. The latter was primarily because the threshold for a priori hypotheses as per COSMIN quality criteria was not achieved. In contrast, all ACQ versions had robust responsiveness to change whereby change scores on the instrument had moderate to strong correlations with QoL instrument change scores, and weak correlations with changes in FEV1% predicted. Further, ACQ versions’ and C-ACT mean score changes exceeded the MCID for patients whose asthma was unstable between study visits.

3.2.2.6 ‘Priority’ composite outcome measures for paediatric severe asthma

CASI received inconsistent to insufficient ratings for all components of content validity, primarily because no patients were involved in its development. The internal consistency and test-retest reliability were rated insufficient. As CASI is multidimensional, internal consistency should have been determined for each unidimensional subscale instead of the total score. There was sufficient ‘low’ quality evidence for construct validity, with moderate correlations between CASI and comparators such as symptom days and asthma control. Sufficient ‘moderate’ quality responsiveness to change was shown by an improvement in the treatment group captured by a higher standardized effect size for CASI compared to symptom days.

4 DISCUSSION

This systematic review used a multi-step approach to identify and determine the quality of the development and measurement properties of ‘priority’ outcome measures for severe asthma, in accordance with the COSMIN guidelines. The current study is unique as it synthesises evidence for outcome measures which are meaningful to patients with severe asthma, and acceptable to other stakeholders, including healthcare professionals, pharmaceutical, and regulatory representatives. From 96 ‘candidate’ outcome measures identified by the literature search, stakeholders selected 55 ‘key’ outcome measures in a modified Delphi exercise, and subsequently 11 and 13 ‘priority’ outcome measures for adult and paediatric severe asthma respectively. The rationale for excluding outcome measures at each step included lack of relevance for effectiveness studies, poor feasibility in terms of cost and accessibility in pan-European healthcare systems, and redundancy with other outcome measures. Of the ‘priority’ outcome measures, the SAQ and C-ACT had the most robust developmental evidence for the severe asthma population. While other ‘priority’ patient-reported and composite outcome measures had data to support validity and reliability, the quality of evidence was limited primarily by the lack of studies with severe asthma participants. This review has been used as a basis for the development of Core Outcome Measures sets for adult and paediatric Severe Asthma (COMSA)⁶⁷.

QoL achieved consensus as a ‘priority’ domain, yet it is used as a secondary outcome in most severe asthma studies⁶⁸. Although QoL only moderately correlates with objective measures⁶⁹, a higher frequency of exacerbations in patients with moderate-to-severe asthma has been associated with deterioration in QoL⁷⁰. Additionally, biologics such as mepolizumab show promising improvements in QoL scores^{71,72}. QoL is the most important domain for patients with severe asthma⁸, outperforming reduction in exacerbation rates. Pertinently, there is an indirect cost patients experience including the burden of daily symptoms resulting in impaired QoL^{73,74}. Future trials should seek to capture this individual disease experience, and ultimately demonstrate QoL benefits beyond the efficacy of a treatment.

Most developmental studies for ‘priority’ QoL measures confounded the construct of QoL with asthma control (symptoms and/or functional status), and were therefore downgraded for comprehensiveness. Similarly, the NIH appraisal highlighted that questionnaires are more likely to assess symptom control instead of QoL impairments experienced due to the ongoing symptoms²⁰. However, the SAQ was developed following the Food and Drug Administration (FDA) guidance¹⁴, and thus captures the impact of both asthma symptoms and treatment on QoL specific to adult severe asthma, illustrated by favourable ratings for content validity. A PROM that can capture the QoL limitations as experienced by children and adolescents with severe asthma remains an unmet need.

The majority of PROMs prioritised in this review are legacy measures. They were developed when different approaches to instrument design were accepted, and it was not compulsory to report the detailed methodological steps undertaken. These measures had inconsistent scores on the modern COSMIN appraisal tool. However, legacy PROMs such as the AQLQ continue

to be implemented in research and practice⁶⁸, amplified by their availability in a variety of languages and modes of administration. In contrast, the SAQ has not been utilised widely in research beyond the original studies, probably because it was recently published, so is only now being incorporated into study protocols. Identifying additional barriers impeding the use of modern instruments should enable their uptake by study sponsors across clinical programs.

The prioritisation of asthma control in this review reflects its positionality as an important treatment goal⁷⁵. An appraisal conducted in 2011 also recommended the asthma control measures selected here as ‘core’ for asthma research¹⁶. Although reviews exist about the ‘priority’ control instruments⁷⁶⁻⁷⁸, none assess the methodological quality of measurement properties for severe asthma. The present synthesis highlights the shortcomings of traditional asthma control tools; the quality of evidence is limited for adult instruments due to the lack of patient involvement in their development^{55,58}, while there is a dearth of studies exclusive to the paediatric severe asthma population validating measures designed for patients ≥ 12 years old^{55,58}. However, these asthma control measures are used in the majority of severe asthma trials⁶⁸, thus investigators should adjust for such limitations when interpreting scores derived from the questionnaires.

Responsiveness to change is a crucial measurement property for any trial endpoint, as poor responsiveness to change can result in false-negative conclusions for the effect of treatment⁷⁹. Some of the priority outcome measures lacked data which could be assessed using the COSMIN toolkit. Of note, responsiveness to change data for the SAQ were published as a research letter after the search date, and thus not included in the current analysis^{80,81}. If these data were included, the SAQ would have sufficient evidence for responsiveness to change, supporting its status as one of the only measures with robust evidence across the measurement properties assessed. The SAQ is also sensitive to detecting benefits of biologics in severe asthma, supporting its use as a primary endpoint in future clinical trials⁸². The MCID⁸³ is not considered a measurement property as per COSMIN guidance, but rather an aspect of interpretability, and therefore its quality was not appraised for the ‘priority’ outcome measures. Nonetheless, MCIDs are imperative for endpoints in effectiveness studies, as they represent a clinically relevant change rather than just a statistically significant one.

Despite the lack of validation data for ‘priority’ clinical and HRU endpoints, they are a cornerstone of severe asthma management in practice. In addition, the European Medicine’s Agency (EMA) recommends clinical outcomes such as lung function should be included at least as secondary endpoints in studies investigating treatments for asthma⁸⁴. Future studies should therefore establish the validity of the ‘priority’ clinical and HRU outcome measures for severe asthma, with a focus on their relevance from a patient-centred standpoint.

Exacerbations are the primary endpoint in most phase III trials investigating new-generation therapies⁸⁵⁻⁸⁸, but the definitions used have immense variability⁸⁹. A composite tool for severe asthma exacerbations⁹⁰ developed in patients taking benralizumab was discussed by the multi-stakeholder panel in Step 3 of the review. However, it was not prioritised primarily because it was developed without any input from patients. The panel ratified the ATS/ERS

definition of exacerbations², but a validated tool to capture severe exacerbations acceptable to relevant stakeholders is a significant research gap.

Around 20-60% of adult patients with severe asthma⁹¹⁻⁹³ are prescribed mOCS, and their associated adverse effects^{2,94} have been shown to impair QoL⁴⁶. Reduction in OCS use is a treatment priority for these patients⁸, yet existing adult QoL tools apart from the SAQ fail to capture the unique treatment burden associated with long-term OCS use⁴⁵. Although mOCS use was also prioritised for paediatric severe asthma, patient representatives voiced that for older adolescents, reduction in OCS use and its associated side effects are a ‘priority’ in some European countries. Healthcare professionals commented that the prioritisation of OCS may differ according to country or healthcare system; mOCS use is not part of the treatment regime for young children in most severe asthma specialist units across Europe. Investigations in paediatric severe asthma cohorts would be valuable in determining the importance of OCS use as a trial endpoint for this population.

Some outcome measures validated in severe asthma, including those utilised for assessing response to biologics, were deprioritised early in the multi-step process. The rationale ranged from lack of patient-centredness and feasibility (poor accessibility in healthcare systems across Europe), to redundancy with other outcome measures. For example, the St George’s Respiratory Questionnaire (SGRQ) has been used in severe asthma trials⁶⁸. However, stakeholders commented the 50-item instrument was developed primarily for Chronic Obstructive Pulmonary Disease; thus, it may be burdensome for patients to complete, and fail to capture the breadth of experiences unique to patients with severe asthma. Likewise, generic QoL questionnaires are paramount as they enable cross-disease comparisons and calculations of health utility⁹⁵. But none were prioritised as they are not as sensitive to impairment and change as asthma-specific QoL measures. Researchers and practitioners should adopt this lens of clinical utility and patient-relevance, as opposed to frequency of use, when selecting instruments for clinical trials and patient-monitoring in practice.

4.1 Strengths and limitations

Our study has several strengths. We used a rigorous multi-step process to identify outcome measures considered a ‘priority’ for severe asthma by four stakeholder groups. Higher weighting was placed on patient representatives’ votes to ensure outcome measure selection at each stage of the study was grounded in a patient perspective. The rigorous COSMIN methodology enabled a standardised quality appraisal of included studies with minimal reviewer bias. Although most included studies had participants with a range of asthma severities, the quality of evidence was evaluated in the severe asthma context. This outlook on the evidence will enable readers to select the most appropriate or robust ‘priority’ outcome measure according to their required domain of assessment. Moreover, we engaged adult and paediatric patient and parent/carer representatives to inform the critical appraisal of content validity of outcome measures. The insights provided by patient representatives ranged from

conceptual (e.g. importance of fatigue as a QoL deficit experienced by adults with severe asthma), to item design (e.g. preference for a global item to evaluate QoL or asthma control).

We limited our review to studies of English language version of outcome measures published in English, and therefore cross-cultural validity (including measurement invariance) could not be appraised. Other studies have reported the validity of other language versions of ‘priority’ PROMs with a higher percentage of patients with

severe asthma than those included in this review, such as QoL96-99 and asthma control99-102 domains. The data reported herein therefore should not be considered exhaustive, but rather an overview of the quality of the available evidence for the severe asthma subgroup. The literature was searched for contemporary ‘candidate’ outcome measures published in a two-year time frame with the safeguard that stakeholders could propose additional outcome measures where justified. The search for studies of ‘priority’ outcome measures was performed in 2020 as the review was undertaken to inform the development of the COMSA⁶⁷. A worst case scenario was adopted for the overall quality of each study since COSMIN appraisal tools use a ‘worst score counts’ principle, whereby high quality scores may be overridden by the lowest scores returned. Lastly, we undertook a narrative synthesis because the heterogeneity in severe asthma definitions, some of the outcome measures such as exacerbations, and consequently study populations precluded a quantitative (meta-) analysis.

4.2 Implications for research and practice

The findings reported herein informed the COMSA consensus study⁶⁷. The implementation of the COMSA will create a more consistent and transparent patient-relevant approach across regulatory, value assessment and market access institutions, as well as in clinical trial development. Currently, in most trials the sole selection criterion for selecting endpoints, especially PROMs, is whether they are widely used, with limited regard for the superiority of the quality of measurement properties. This evidence synthesis on the quality of measurement properties should aid researchers and practitioners to choose the most appropriate outcome measures to evaluate treatment response. Further, this review offers insights into the developmental limitations of historically used ‘priority’ QoL and asthma control measures for the severe asthma population. Poor content validity can indirectly hamper the quality of other measurement properties, including responsiveness to change. Regulatory bodies should therefore take caution when interpreting results of trials using legacy endpoints to investigate new-generation therapies for severe asthma. The lack of validation data for clinical and HRU endpoints warrants studies which implement standardised approaches to evaluate their measurement properties in participants with severe asthma.

5 CONCLUSION

Outcome measures with robust measurement properties and practical feasibility are a pre-requisite for evidence-based healthcare. This review identified 96 ‘candidate’ outcome measures and used a multi-stakeholder consensus process to select 24 ‘priority’ outcome measures for adult and paediatric severe asthma. Clinical and HRU endpoints are the mainstay as per the regulatory demands for approval of medications, but the validity of these endpoints should be established in adult and paediatric severe asthma as a matter of some urgency. Of the included patient-reported and composite outcome measures, only the SAQ and C-ACT were developed with input from severe asthma patients, supported by predominantly sufficient ‘moderate’ quality evidence for the measurement properties assessed. Further validation in clinical trials, and translation to other languages should enable the SAQ to become a status quo QoL endpoint for phase III studies. Despite the ‘low’ to ‘very low’ quality developmental evidence for legacy QoL and asthma control measures, most had sufficient evidence for the measurement properties appraised except responsiveness to change. There is an urgent need to follow contemporary standards^{14,103,104} when developing new outcome measurement instruments. To that end, researchers should seek to develop a scale for paediatric QoL based on extensive qualitative input from patients with severe asthma and subsequently validate it in studies with good methodological quality.

Authors’ contributions:

Study concept and design: GR, AR. Conduct and analysis of modified Delphi exercise, multi-stakeholder meetings, and online voting: AR, EK. Literature searches, data extraction, and COSMIN assessments: AR, EK. Drafting of the original manuscript: AR, EK, GR. All authors provided critical review of the manuscript and approved the final version.

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Disclaimer:

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Conflict of interest:

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TABLES

Table 1. Summary characteristics of priority patient-reported and composite outcome measures.

Outcome measure (year)	Target population	Patient/ carer report	Mode(s) of administration	No. of items	Recall period	Response format(s)	Scoring method	Time to complete	Original language, translations*	License and costs
Quality of life outcome measures for adults										
AQLQ (1993) ³⁵	17-70 years	Patient	Self-complete, interviewer, paper, online, electronic devices	32 (4 sub)	2 weeks	7-point Likert scales. 1 = severely impaired, 7 = not impaired at all.	4 subscales. Overall score: mean of responses to all items, range 1-7.	5-10 minutes	English (North America), 86 translations	Copyrighted by QoL Technologies Ltd. Paper version: free for non-commercial practice and research. One-time fee for commercial use. Electronic version: user fee for commercial and academic use.
AQLQ-5 (1999) ⁴²	18-70 years	Patient	Self-complete, interviewer, paper, online, electronic devices	32	2 weeks	Same as AQLQ	Same as AQLQ	5-15 minutes (4-5 minutes according to Qoltech web site ¹⁰⁵)	English (North America), 108 translations	Same as AQLQ
Mini-AQLQ (1999) ⁴⁴	18-65 years	Patient	Self-complete, interviewer, paper, electronic devices	15	2 weeks	7-point Likert scale. 1=all the time, 7=none of the time.	Same as AQLQ	3-4 minutes	English (North America), 83 translations	Same as AQLQ
SAQ (2018) ⁴⁵	16-78 years	Patient	Self-complete, paper	SAQ: 16-items* SAQ-global: 1	2 weeks	16-items: 7-point Likert scale. 1=very, very difficult, 7=no problem. SAQ global: 100-point Borg-type	SAQ score: mean of responses to 16 items, range 1-7. SAQ-global score: range 0-100.	3-6 minutes	English (UK), 2 translations	Copyrighted by University of Plymouth and University Hospitals Plymouth NHS Trust. Free for non-commercial clinical practice and

Outcome measure (year)	Target population	Patient/ carer report	Mode(s) of administration	No. of items	Recall period	Response format(s)	Scoring method	Time to complete	Original language, translations*	License and costs
						scale. 0=no QoL, 100=perfect QoL.				research. Fee may apply for funded research, healthcare organizations, commercial users.
Quality of life outcome measures for children										
PAQLQ (1996) ⁴⁷	7-17 years	Patient	Self-complete, interviewer, paper	23	1 week	7-point Likert scale. 1=severe impairment, 7=no impairment.	3 subscales. Overall score: mean of responses to all items, range 1-7.	10-15 minutes at initial visit. 5-10 minutes at follow-up visit.	English (North America), 62 translations	Copyrighted by QoL Technologies Ltd. Free for use in non-commercial practice and research. Otherwise, there is a one-time fee.
PAQLQ-5 (2012) ⁵²	7-17 years	Patient	Self-complete, interviewer, paper, electronic devices	23	1 week	Same as PAQLQ	Same as PAQLQ	Not reported	English (North America), 64 translations	Same as PAQLQ
Mini-PAQLQ (2012) ⁵²	7-17 years	Patient	Self-complete, interviewer, paper, electronic devices	13	1 week	7-point Likert scale. 1= maximum impairment, 7= no impairment.	Same as PAQLQ	Not reported	English (North America), 18 translations	Same as PAQLQ
Asthma control outcome measures for children										
C-ACT (2007) ⁶⁹	Children / carer of children aged 4-11 years	Patient and carer	Self-complete, interviewer, paper, web-based	7	4 weeks	Patient report: 4-point Likert and pictorial scale. 0= 'very bad', 3='very good'. Carer report: 6-point Likert scale. 0=	Total score range: 0-27. Score ≥19 indicates well-controlled asthma.	5 minutes (web-based version)	English (USA), 27 translations	Copyrighted by GlaxoSmithKline Ltd. Free for non-commercial clinical practice and research. Fee may apply for commercial use.

Outcome measure (year)	Target population	Patient/ carer report	Mode(s) of administration	No. of items	Recall period	Response format(s)	Scoring method	Time to complete	Original language, translations*	License and costs
						'everyday', 5= 'not at all'.				
Asthma control outcome measures for adults and children										
ACQ-7 (adults: 1999 ⁵⁸ , children: 2010 ⁶¹)	≥ 6 years	Patient and clinician	Self-complete (≥11 years), interviewer (6-10 years), paper, interactive web, electronic devices.	7 (Patient: symptom control, SABA use. Clinician: FEV ₁ % predicted)	1 week	7-point Likert scale. 0=no impairment, 6= maximum impairment. FEV ₁ % predicted scored on 7-point Likert scale.	Total score: mean of responses to all items, range 0-6.	3 minutes	For adults: English (North America) For children: English (UK), 111 translations	Copyrighted by QoL Technologies Ltd. Paper version: free for non-commercial practice and research. One-time fee for commercial use. Electronic version: user fee for commercial and academic use.
ACQ-6 (adult: 2001 ⁵⁹ , children: 2010 ⁶¹)	Same as ACQ-7	Patient	Same as ACQ-7	6	Same as ACQ-7	7-point Likert scale. 0=no impairment, 6= maximum impairment.	Same as ACQ-7	Not reported	Same as ACQ-7	Same as ACQ-7
ACQ-5 (adult: 2001 ⁵⁹ , children: 2010 ⁶¹)	Same as ACQ-7	Patient	Same as ACQ-7	5	Same as ACQ-7	Same as ACQ-6	Same as ACQ-7	Not reported	Same as ACQ-7	Same as ACQ-7
ACT \uparrow (2004) ⁵⁵	≥12 years	Patient	Self-complete, interviewer, paper, web-based, telephone, mail.	5	4 weeks	5-point Likert scale. Items about symptoms and activities: 1=all the time, 5=not at all. Self-rating of control: 1=not	Total score range: 5-25. Score ≥19 indicates well-controlled asthma.	1-2 minutes	English (USA), 179 translations ¹⁰⁶	Copyrighted by Quality Metric Inc. Permission required for use.

Outcome measure (year)	Target population	Patient/ carer report	Mode(s) of administration	No. of items	Recall period	Response format(s)	Scoring method	Time to complete	Original language, translations*	License and costs
						controlled at all, 5=completely controlled.				
Composite outcome measures for adults										
ACCI (2008) ⁶⁵	≥12 years	Patient and clinician	Self-complete, paper	Control subscale: 5	Control subscale: 1 week (2 weeks for night-time awakening item). Acute care, bother and 'direction of symptoms' subscales: 'since the last clinical visit'.	Multiple choice. Colour coded from green (best), to red (worst). One open-ended question.	Acute care, bother and 'direction of symptoms' subscales: Responses converted to numbers; ↑ score = ↓ health status. Control subscale scored by clinician: 1) 4 categories, ranging from mild intermittent (controlled) to severe-persistent (uncontrolled). 2) Total score assigned to each response, ranging 0-19, ↑ score = ↓ control. 3) Yes / no rating of items as 0 (controlled) or 1 (uncontrolled). Summed to provide a problem index, 0-5. ↑ score = ↓ control.	5-7 minutes	English (USA), Portuguese (Brazil)	Not reported.
Composite outcome measures for children										
CASI (2012) ⁶⁶	≥ 6 years	Patient and clinician	Interviewer, paper, online calculator available	5 domains: day symptoms and albuterol use, night symptoms and albuterol use, and albuterol	2 weeks: day symptoms and albuterol use, night symptoms and albuterol use, and controller	Multiple choice	Responses converted to points with different weights. Total score: sum of points of all items, range 0-20. ↑ score indicates ↑ level of severity.	Not reported	English (USA)	Free to use.

Outcome measure (year)	Target population	Patient/ carer report	Mode(s) of administration	No. of items	Recall period	Response format(s)	Scoring method	Time to complete	Original language, translations*	License and costs
				use, controller medicine, lung function, exacerbations.	2 months.	exacerbations				

AQLQ, Asthma Quality of Life Questionnaire; AQLQ-S, Asthma Quality of Life Questionnaire Standardized; Mini-AQLQ, Mini Asthma Quality of Life Questionnaire; SAQ, Severe Asthma Questionnaire; QoL, Quality of Life; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; PAQLQ-S, Paediatric Asthma Quality of Life Questionnaire Standardized; Mini-PAQLQ, Mini Paediatric Asthma Quality of Life Questionnaire; C-ACT, Childhood Asthma Control Test; ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; ED, Emergency Department; FEV₁, forced expiratory volume in 1 second; ACCI, Asthma Control and Communication Instrument; CASI, Composite Asthma Severity Index; QoL, Quality of Life; NA, Non-applicable. *: The number of translations is an estimate sourced from sites and manuals of the instruments available in English (not from the systematic literature search). Also, evidence for the validity of the translated versions has not been synthesised as it was outside the scope of the current review.

Table 2. Quality of evidence for measurement properties of priority outcome measures for severe asthma.

Outcome measure	Measurement property															
	Relevance*		Comprehensiveness*		Comprehensibility*		Internal consistency		Test-retest reliability		Criterion validity**		Construct validity		Responsiveness to change	
	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE
<i>Adult</i>																
<i>Quality of life</i>																
AQLQ ^{35-41,54}	±	⊕○○○ ^{ALC}	-	⊕○○○ ^{ALC}	+	⊕⊕○○ ^C	+	⊕⊕⊕○	+	⊕○○○ ^C			-	⊕⊕○○ ^C	+	⊕⊕○○ ^C
AQLQ-S ^{41-43¶}	±	⊕⊕○○ ^C	-	⊕⊕○○ ^C	+	⊕○○○ ^{ALC}	+	⊕⊕○○ ^C	+	⊕○○○ ^{ALC}			-	⊕⊕○○ ^C	+	⊕○○○ ^{ALC}
MiniAQLQ ^{41,44¶}	±	⊕⊕○○ ^C	-	⊕○○○ ^C	+	⊕⊕○○ ^C	+	⊕⊕○○ ⁰	+	⊕⊕○○ ⁰	+	⊕○○○ ⁰	+	⊕○○○ ^{AL0}	?	?
SAQ ^{45,46,80,81}	+	⊕⊕⊕○	+	⊕⊕⊕○	+	⊕⊕⊕○	?		+	⊕⊕⊕○			+	⊕⊕⊕⊕	?	?
<i>Asthma control</i>																
ACT ^{55,57}	±	⊕○○○ ^C	-	⊕○○○ ^{ALC}	-	⊕○○○ ^{ALC}	+	⊕⊕⊕○	+	⊕⊕○○ ^C			-	⊕⊕○○ ^C	-	⊕○○○ ^C
ACQ5 ⁵⁸⁻⁶⁰	±	⊕○○○ ^C	-	⊕○○○ ^C	-	⊕○○○ ^{ALC}	+	⊕⊕⊕○	+	⊕⊕○○ ^C	+	⊕⊕⊕○ ^C	-	⊕○○○ ^C	-	⊕○○○ ^C
ACQ6 ⁵⁸⁻⁶⁰	±	⊕○○○ ^C	-	⊕○○○ ^C	-	⊕○○○ ^{ALC}	+	⊕⊕⊕○	+	⊕⊕○○ ^C	+	⊕⊕⊕○ ^C	-	⊕○○○ ^C	-	⊕○○○ ^C
<i>Composite</i>																
ACCI ^{65††}	+	⊕○○○ ^{ALC}	-	⊕○○○ ^{ALC}	+	⊕○○○ ^{ALC}	-	⊕○○○ ^C	?				+	⊕○○○ ^C	?	
<i>Children and adolescents</i>																
<i>Quality of life</i>																
PAQLQ ^{47,49,51,52}	±	⊕⊕○○ ^C	±	⊕○○○ ^{ALC}	+	⊕⊕○○ ^C	+	⊕⊕○○ ⁰	+	⊕⊕⊕○			+	⊕⊕⊕○	+	⊕⊕○○ ^C
PAQLQ-S ^{47,50,52¶}	±	⊕⊕○○ ^C	±	⊕○○○ ^C	±	⊕○○○ ^C	+	⊕○○○ ⁰	+	⊕⊕○○ ⁰			+	⊕⊕○○ ⁰	+	⊕○○○ ⁰
MiniPAQLQ ^{51,53¶}	±	⊕○○○ ^A	±	⊕○○○ ^A	±	⊕○○○ ^C	-	⊕⊕⊕○	+	⊕⊕○○ ⁰	+	⊕⊕○○ ⁰	+	⊕⊕⊕○	?	?
<i>Asthma control</i>																
ACT ^{55,56}	±	⊕○○○ ^C	-	⊕○○○ ^{ALC}	-	⊕○○○ ^{ALC}	+	⊕⊕○○	+	⊕○○○ ^C			+	⊕○○○ ^C	-	⊕○○○ ^C
CACT ^{63,64}	+	⊕⊕⊕○ ^C	±	⊕○○○ ^{ALC}	+	⊕⊕⊕○ ^C	+	⊕⊕⊕○	+	⊕⊕⊕○			+	⊕⊕○○ ^C	+	⊕⊕○○
ACQ5 ^{58,60,61,107†}	±	⊕○○○ ^C	-	⊕○○○ ^C	+	⊕⊕○○ ^C	+	⊕⊕○○	+	⊕○○○ ^C	+	⊕⊕○○	+	⊕○○○ ^C	+	⊕○○○ ^C

Outcome measure	Measurement property															
	Relevance*		Comprehensiveness*		Comprehensibility*		Internal consistency		Test-retest reliability		Criterion validity**		Construct validity		Responsiveness to change	
ACQ6 ^{58,60,61,107†}	±	⊕○○○ ^c	-	⊕○○○ ^{Mc}	+	⊕⊕○○ ^c	+	⊕⊕○○	+	⊕○○○ ^c	+	⊕⊕○○	+	⊕○○○ ^c	+	⊕○○○ ^c
ACQ7 ^{58,60,62,107†}	±	⊕○○○ ^c	-	⊕○○○ ^{Mc}	+	⊕⊕○○ ^c	+	⊕⊕○○	+	⊕○○○ ^c			+	⊕○○○ ^c	+	⊕○○○ ^c
<i>Composite</i>																
CASI ⁶⁶	±	⊕○○○ ^c	-	⊕○○○ ^c	-	⊕○○○ ^c	-	⊕○○○ ^c	-	⊕○○○ ^c			+	⊕⊕○○ ^c	+	⊕⊕○○

AQLQ, Asthma Quality of Life Questionnaire; AQLQ-S, Asthma Quality of Life Questionnaire Standardized; Mini-AQLQ, Mini Asthma Quality of Life Questionnaire; SAQ, Severe Asthma Questionnaire; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; PAQLQ-S, Paediatric Asthma Quality of Life Questionnaire Standardized; Mini-PAQLQ, Mini Paediatric Asthma Quality of Life Questionnaire; ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; ACQ-5: items about symptom control only; ACQ-6: items about symptom control, and rescue medication use; ACQ-7: items about symptom control, rescue medication use, and forced expiratory volume in 1 second (FEV₁) ACCI, Asthma control and communication instrument; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; COSMIN, COnsensus-based Standards for the selection of Measurement Instruments.

Ratings of quality of results for measurement properties was done against COSMIN quality criteria^{17,32}: +, sufficient; -, insufficient; ?, indeterminate; ±, inconsistent (for development criteria only). The review team formulated *a priori* hypotheses for appraising construct validity and responsiveness to change; hypotheses included the expected direction and magnitude of correlations between the priority outcome measure and other instruments, and expected mean differences in scores between groups. A sufficient rating was awarded if ≥75% of the hypotheses were fulfilled for pooled results of the measurement property. Ratings are based on data from the studies published in English for the English language version of the instrument only. See online supplement for detailed results.

Certainty of evidence was evaluated using the modified GRADE approach^{17,34}. For content validity, this considers: A. risk of bias, B. inconsistency, C. indirectness, and for grading other measurement properties, an additional factor of D. imprecision.

*: Results are a combination of data from the publication (views of patients and/or professionals), and ratings by review team.

** : Criterion validity was not assessed for the full-versions of patient-reported and composite instruments as there is no gold standard.

†: There is moderate and high concordance between this shortened/standardised version and the original instrument.

††: Responsiveness data were published after the search was run. See discussion for further details.

§: Internal consistency was only evaluated for the total scale score of the SAQ assessed to be multi-dimensional by the review team, and thus not eligible for assessment as per COSMIN methodology. A study published after the search was run established subscales for the SAQ and reported their internal consistency⁸⁰.

#: Responsiveness assessed for overall score, symptoms, and emotional functioning subscales using minimal important difference (MID) established for original questionnaire. The responsiveness of the activity subscale could not be calculated using the MID established for the original questionnaire as it has been modified (patient-specific activities replaced with standardised activities).

‡: Responsiveness could not be assessed as a Minimal Clinical Important Difference (MCID), or MID has not been established for this outcome measure.

‡: Development of ACQ versions for the paediatric population was presented at a conference.

††: The ACCI developmental process was presented at a conference^{108,109}.

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FIGURE LEGENDS

Figure 1.

Overview of the multi-step process for identifying and appraising patient-centred priority outcome measures for severe asthma.

FIGURE 1:

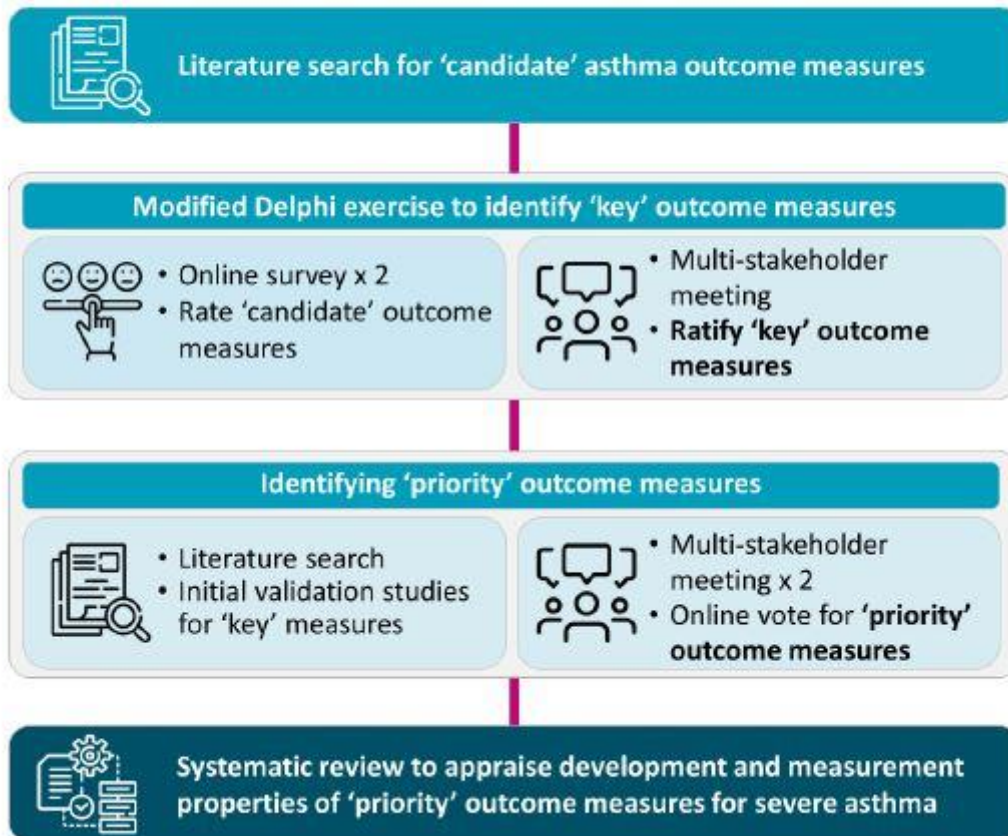


Figure 2.

Priority outcome measures for adult and paediatric severe asthma. AQLQ, Asthma Quality of Life Questionnaire; AQLQ-S, Asthma Quality of Life Questionnaire Standardized; Mini-AQLQ, Mini Asthma Quality of Life Questionnaire; SAQ, Severe Asthma Questionnaire; QoL, Quality of Life; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; PAQLQ-S, Paediatric Asthma Quality of Life Questionnaire Standardized; Mini-PAQLQ, Mini Paediatric Asthma Quality of Life Questionnaire; C-ACT, Childhood Asthma Control Test; ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; ACCI, Asthma Control and Communication Instrument; CASI, Composite Asthma Severity Index; FEV₁, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; mOCS, maintenance oral corticosteroids, *: Defined by the ATS/ERS 2014 statement as annual frequency of events requiring systemic corticosteroids for ≥ 3 days and/or a hospitalisation/emergency room visit requiring systemic corticosteroids.

FIGURE 2:

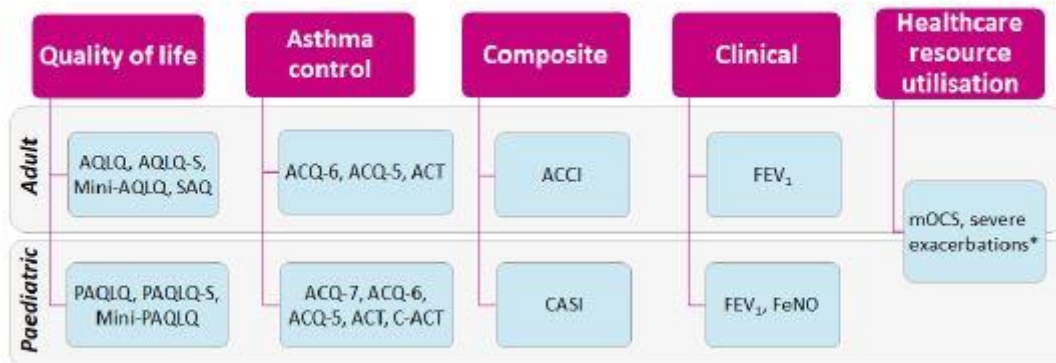


Figure 3.
PRISMA flow diagram for study selection. PROM, Patient Reported Outcome Measure.

FIGURE 3:

