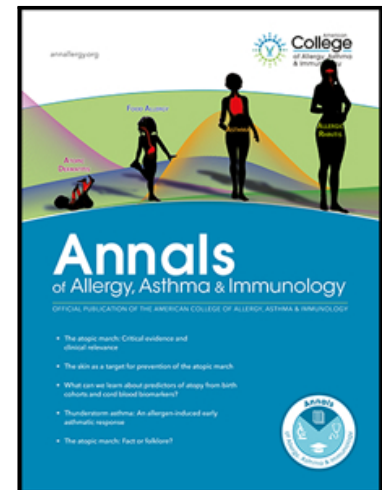


A multi-stakeholder Delphi consensus core outcome set for clinical trials in moderate-to-severe asthma (coreASTHMA)

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Keywords: Asthma, clinical trials, outcomes, comparative effectiveness research

Abbreviations

AC – Advisory Committee

ACQ - Asthma Control Questionnaire

ACT – Asthma Control Test

AE - Adverse Effects

AQLQ - Asthma Quality of Life Questionnaire

ATS/ERS - European Respiratory Society and American Thoracic Society

COMET - Core Outcome Measures in Effectiveness Trials

COS - Core outcome set

ED – Emergency department

FEV1 - Forced expiratory volume-one second

GINA - Global Initiative for Asthma

HRQoL - Health-related quality of life

HTA - Health Technology Assessor

ICS - Inhaled corticosteroids

OCS - Oral corticosteroids

PFT - Pulmonary function tests

PRO - Patient-reported outcome

QoL - Quality of life

Background:

Treatments for long-term control of asthma have improved and include a promising but expensive class of biologic therapies. However, the clinical trials evaluating these and other novel treatments have utilized a variety of different outcomes to evaluate efficacy. The evolution of asthma care calls for a re-examination of outcomes that are most important to patients and other stakeholders.

Objective:

The coreASTHMA project sought to develop a core set of outcomes to be measured in phase 3 and phase 4 clinical drug trials in patients with moderate-to-severe asthma. Methods:

We utilized a robust and in-depth multi-stakeholder consensus process bringing together patients, clinicians, regulators, payers, health technology assessors, researchers, and product developers to reach consensus on outcomes. We employed a modified Delphi method to reach consensus, an approach adapted from the Core Outcome Measures in Effectiveness Trials Initiative aligned with contemporary methodological standards for core outcome set development.

Results:

The following outcomes were included in the final core set: severe asthma exacerbation, change in asthma control, asthma-specific or severe asthma-specific quality of life, asthma-specific hospital stay (i.e. >24 hour stays at any level of care) or admission, and asthma-specific emergency department visit.

Conclusion:

These five outcomes represent a minimum set of core outcomes for use in phase 3 and phase 4 clinical drug trials in moderate-to-severe asthma. Consistent collection of these outcomes as minimum, independent of whether additional heterogeneous primary or secondary outcomes are included, will allow for meaningful comparisons across clinical trials of the effect of asthma therapies.

Introduction

Asthma is a chronic disease impacting quality of life (QoL), daily functioning, and productivity. Daily symptoms can restrict ability to participate in physical, social, or school/work activities. An asthma exacerbation is a stressful and often costly experience for patients and their families.¹ Although symptoms can usually be controlled to enable an active and healthy life, there remains a subset of patients with severe disease. Among the 20 million adults and 6 million children with asthma in the U.S., <10% experience severe asthma.^{2,3} Yet, these patients account for a majority of the \$80 billion annual asthma-related costs, including medications, side effects incurred by oral corticosteroid (OCS), healthcare utilization, missed school/work days, and asthma-related mortality.⁴

Rapid introduction of new treatments, including biologics, has led to tremendous advances in management of refractory asthma. Although pivotal trials have included exacerbations as an outcome, more broadly clinical trials have utilized a variety of different outcomes to evaluate efficacy. The heterogeneity of outcomes in clinical trials has limited assessment of the comparative effectiveness of one agent to another. The evolving nature of asthma care calls for a re-examination of outcomes that are most important to patients and other key stakeholders. The importance of this is highlighted by a minimum set of outcomes that has been recently been established for asthma patient registries.⁵ Furthermore, an Asthma Outcomes workshop was convened in 2012 to provide recommendations on outcomes within seven domains for broad use in clinical research in asthma.⁶ Although this workshop resulted in an important expert consensus on outcomes, a voting methodology was not utilized and there was not patient representation. Meaningful and transparent engagement of patients, clinicians, regulators, payers, industry, and other key stakeholders through the Delphi methodology confers unique advantages of facilitated discussion and prevents dominant individuals from controlling the

conversations.⁷⁻⁹ This will allow identification of high priority outcomes that can be consistently incorporated into clinical trial designs and evidence-based clinical and policy decisions.

Given this gap, the Green Park Collaborative, in partnership with the Allergy & Asthma Network, brought together patients, clinicians, regulators, payers, health technology assessors (HTA; who consider evidence regarding clinical effectiveness, safety, and cost-effectiveness), researchers, and product developers to establish the coreASTHMA project which sought to develop a core set of outcomes to be measured in phase 3 and 4 clinical drug trials for patients with moderate-to-severe asthma in adults and children aged $\geq$ five years. A core outcome set (COS) is a minimum set of outcomes that should be measured and reported in all clinical trials for a specific condition.¹⁰ The decision to include moderate-to-severe asthma stemmed from acknowledging variability in defining, capturing, and diagnosing severe asthma in different healthcare contexts. However, we recognize patients with severe asthma have a unique disease experience, with its own set of burdens that is not well represented in existing evidence and value assessments.¹¹ For the purpose of this project, we used the established severe asthma definition from the American Thoracic Society/European Respiratory Society's (ATS/ERS) guidelines which is consistent with the Global Initiative for Asthma (GINA) definition, and given the absence of a definition of moderate asthma, this was defined by the Global Initiative for Asthma (GINA) steps 3-4 guidelines.^{14,15} A multi-stakeholder consensus process was utilized to reach consensus on outcomes for a COS.

Methods

Overview

coreASTHMA utilized a modified Delphi method to reach multi-stakeholder consensus. This approach was adapted from the Core Outcome Measures in Effectiveness Trials (COMET) Initiative and

is commensurate with the most current methodological standards for COS development (**Figure 1**).¹⁶

The project launched in October 2019 and included four stages over an eight-month period: 1) Stakeholder recruitment and training, 2) Background research including identification of outcomes for consideration, 3) Delphi surveys to condense and prioritize the outcome list, and 4) A consensus meeting for discussion of the core set.

Stakeholder Recruitment and Training

Advisory Committee

A non-voting Advisory Committee (AC), comprised of 13 members with 8 clinician-researchers (practicing physicians that conduct research), 2 researchers (non-clinician researchers), 2 patient advocates and 1 regulator, was convened to provide guidance and feedback. Members were invited given their background in asthma research, clinical practice leadership and patient advocacy. Patient advocates are members from Allergy & Asthma Network. AC's roles included voluntarily advising on development and refinement of initial outcomes list, advising on composition of proposed multi-stakeholder Delphi panel, and deliberating on proposals for adding or combining outcomes after each voting round. The AC's preclusion from voting in the Delphi surveys maintained separation and transparency between project oversight and consensus development process.

Delphi Panel

The Delphi panel was the voting body tasked with discussing and voting on outcomes. All significant decisions made by the project team and AC, such as revisions to outcomes list or definitions, were presented to panel for feedback and approval prior to implementation. A multi-stakeholder group was invited, including patients or patient advocates, clinician-researchers, researchers, HTA, payers, regulators (governmental and private sectors), and representative from pharmaceutical companies.

Patients or patient advocates were identified and invited through patient organization partner. The panel was balanced for a diverse set of expertise; HTA is expert in evaluating evidence regarding clinical effectiveness, safety, and cost-effectiveness to inform policy decision making; two representatives from each participating pharmaceutical company with an asthma product in the pipeline were experts in clinical development, market access, or health economic outcome research. However, the total number of industry votes was less than total number of votes from non-industry participants (**Table 1**).

Orientation and Training

Participants were invited to introductory and Delphi orientation webinars that provided details on methods and project goals. The coreASTHMA project team also prepared two training webinars designed for patients and patient advocates introducing concepts of clinical trial design, outcome selection, COS in research, and Delphi process.

Identification of Outcomes

Literature Review and Interviews

A list of candidate outcomes was compiled based on a review of literature on Cochrane Library and clinicaltrials.gov utilized to identify outcomes already used in asthma trials. The list was supplemented by key informant interviews and suggestions from AC members and Delphi panel.¹⁷ Key informant interviews with 5 patient advocacy groups, 4 clinicians/researchers, 3 payer groups, 2 HTA groups and 8 pharmaceutical companies provided perspectives regarding the most important outcomes to measure. Interviewees were invited to suggest novel outcomes that may not yet be in the literature and share insights into the utilization and adequacy of existing outcomes. Novel outcomes were added to the candidate list and insights were used to frame outcome list refinement.

Outcome selection, grouping, and refinement

Outcomes relating to unintended consequences of interventions (e.g. adverse events) were excluded as these outcomes are required to be reported to regulators.¹⁸ The initial outcomes list with draft definitions was circulated to the AC for review and refinement. Questions regarding redundant outcomes, accurate grouping, and sufficient definitions were posed to the committee. The list was subsequently sent to Delphi panelists for comments and suggestions. Updates to the outcomes list and the rationale for these decisions were shared with the panel to ensure a fully transparent process.

Delphi Surveys

Delphi voting

Three rounds of online Delphi voting were conducted, two preceding and one following the consensus meeting, using Qualtrics XM software (Qualtrics, Provo, UT). Participants were asked to rate the importance of including each outcome in clinical trials for moderate-to-severe asthma using a scale from 1 to 9 (**Table 2**). Participants could also select “Don’t know/No opinion” if they had no opinion, were unsure of the outcome’s importance, or otherwise had uncertainties that precluded an opinion.

Delphi analysis

Survey responses were analyzed based on pre-determined consensus criteria (**Table 3**). To ensure outcomes important to patients were not eliminated prior to the consensus meeting and final voting round, a “patient-important” criterion was included the first two rounds of voting. This criterion means that any outcome voted as critical to include by patients was included irrespective of its score from all participants.

Before rounds 2 and 3 of Delphi voting, participants were given individual and summary reports (**eFigure 1**) from the previous round. Summary reports included a table containing percentage of voters by voting category and mean score stratified by stakeholder group for each outcome. Scatterplots were

also provided to show votes by each stakeholder group. Individual reports displayed the participant's rating for each outcome, highlighting outcomes where their rating was ≥ 2 points different from the mean score. Analyses were performed with R version 3.6.3.

Consensus meeting

A virtual consensus meeting was held between Delphi round 2 and 3, attended by 39 of 45 Delphi panelists (87%) and 8 of 13 AC members (62%). The purpose was to help participants better understand different stakeholder views about important outcomes in asthma clinical trials and bring people closer to a consensus on a final COS.

The consensus meeting consisted of three sessions: 1) Physiological/Clinical Outcomes, 2) Resource Use Outcomes, and 3) Functional Outcomes and Patient Reported Outcomes (PROs). Each session started with a brief expert presentation on Delphi Round 2 voting results, followed by breakout discussions and a full group discussion led by an expert facilitator. Breakout and main group discussions focused on retained outcomes from Delphi Round 2 and key issues for debate. Participants had the opportunity to propose new or more succinct outcomes (with rationale) and suggest combinations of outcomes or refinements to outcome definitions.

Results

Identification of Outcomes

A total of 181 clinical trial records on clinicaltrials.gov and 57 Cochrane Reviews were identified in our targeted literature review. Of these, 74 clinical trial records and 36 Cochrane Reviews were excluded based on the type of intervention or outcome measures, the age of study population, and the scope of disease. An additional 3 clinical trials and 8 Cochrane Reviews were excluded given they assessed acute exacerbation therapies. Outcomes from a total of 117 studies were extracted and

recorded.¹⁷ From these 117 studies, 111 distinct outcomes were identified. An additional 35 outcomes were added from interviews with key informants, selected literature review on asthma outcome measures, patient-important outcome development, and patient preference studies. This list of 146 outcomes was then presented to AC for review.

In response to AC feedback, two major changes were made to the candidate list of outcomes: 1) Biomarker outcomes were removed as they classify patients (e.g. “eosinophilic asthma”), verify mechanism of action, or may be used as inclusion criteria for trials or therapies, and 2) Outcomes related to adverse effects (AEs) of oral and inhaled corticosteroid were removed -- though patient-important -- after feedback that they do not necessarily have a role as trial outcomes. After multiple rounds of refinement, the candidate list for the Round 1 Delphi survey included 88 outcomes in the following domains: physiological/clinical, functional, resource use, and mortality/survival (**eTable 1**).

Delphi Surveys and Consensus Meeting

The Delphi panel had a response rate of >90% each round (**eTables 2-4**). The outcome list for first round of Delphi voting included 88 outcomes and 7 of them were retained after 3 rounds of voting (**Figure 2**). Additionally, voter feedback from surveys and as a result of group discussions during the consensus meeting prompted revisions to the outcome list (**Table 4**). All proposed changes were circulated to the Delphi panel and AC for review before implementation with no objections.

Final Core Outcome Set

The following outcomes reached the threshold for inclusion in the final core set and are recommended for use in all phase 3 and phase 4 clinical drug trials for moderate-to-severe asthma (**Table 5**): severe asthma exacerbation, change in asthma control, asthma-specific or severe asthma-specific QoL, asthma-specific hospital stay (>24 hours at any level of care) or admission, and asthma-specific emergency department (ED) visit.

Asthma-specific hospital stay and asthma-specific hospital admission were originally two separate outcomes. However, given discussions with the AC, clinical consultants and patient advocacy partners, it was proposed outcomes be combined due to redundancy and variability among hospital admission protocols. Another suggestion was to exclude asthma-related death since it is generally reported to fulfill regulatory requirements. Hence, while asthma-related death reached high consensus, it was not included in the final COS.

Discussion

The creation of this COS for moderate-to-severe asthma utilized a methodologically robust, transparent, multi-stakeholder consensus process. This methodology confers the unique advantage of incorporating key perspectives from in-depth engagement of those relying on evidence to make decisions. Furthermore, our consensus meeting brought patient perspective to the forefront and allowed for stakeholders to interact across disciplines in ways trial development and drug approval often do not.^{19,20}

Frequency of severe exacerbations, defined by ATS/ERS criteria,¹² was highly prioritized with nearly unanimous agreement. However, this outcome has only been reported in approximately 25% of moderate-to-severe asthma trials.¹⁷ Despite being characterized as a key endpoint, its definition in trials has been highly variable.²¹⁻²³ Similarly, change in asthma control has been reported in under half of trials we previously reviewed.¹⁷ The Delphi panelists expressed that composite outcomes (e.g. ACT) encompassing multiple symptoms are preferable to single outcome measures.^{24,25} However, some questioned the relative usefulness of instruments that don't enable reporting of individual components. All individual outcomes of composite scores were also included initially for voting but none were retained in the final COS. The only individual outcome that made it to Round 3 voting was chest tightness/pain, which was retained as "patient-important." During the consensus meeting, patients

expressed this outcome was not necessarily intrinsically core, but rather a key symptom for self-monitoring asthma control underrecognized compared to more typical features (e.g. cough, dyspnea, wheezing). In the final round of voting, this did not meet criteria for inclusion in the final COS and 40% of patients voted it as critical to include in the COS.

Asthma-specific – or when applicable, severe asthma-specific – QoL possessed nearly unanimous agreement during consensus meeting as critically meaningful. Discussion focused on how best to measure this particular outcome. The group preferred more granular, domain-specific reporting over summary scores and thought current QoL measures (e.g. Asthma Quality of Life Questionnaire), though widely used, do not effectively capture symptom impact on QoL.²⁶ Participants communicated that current QoL measures are difficult to interpret and don't convey meaningful information to patients and physicians.

Two healthcare utilization outcomes were retained: asthma-specific hospital stay/admission and asthma-specific ED visit. Asthma-specific hospital stay, defined as >24 hours of in-patient care, was added following consensus meeting discussions that deemed outcomes related to health system utilization (i.e., asthma-specific hospital admission, asthma-specific ICU admission, and asthma-specific unscheduled visit to a health facility) insufficient. Those were thought to be insufficient given the following limitations: level of care is not as relevant as being hospitalized, definition of “admission” varies, and it is challenging and less relevant to discern planned versus unplanned visits. Asthma-specific ED visit was highlighted as important for capturing need for emergency care. However, we acknowledge confounders exist to pursuing ED care. In countries without a nationalized healthcare system, the likelihood of obtaining care at an ED can be influenced by insurance status, socioeconomic status, race, ethnicity, and/or primary care access.²⁷⁻³³ In contrast, ED presentation for acute care is lower in countries with a nationalized healthcare system.³⁴⁻³⁵

The absence of certain outcomes merits discussion. Pulmonary function tests (PFTs), included as an outcome in at least one-third of studies we reviewed,¹⁷ are notably absent. While 3 PFT outcomes progressed to Round 3 voting (pre-bronchodilator lung function, post-bronchodilator lung function, and FEV1/FVC ratio) and a robust consensus meeting discussion focused on their respective merits, none of them ultimately met inclusion threshold. The two groups in which >70% of participants voted pre-bronchodilator lung function as critically important were regulators (100%) and industry (80%). This underscores its role as an endpoint for drug approval, however, given the patient-centered orientation of this project, demonstrates lung function is viewed as less meaningful by patients and clinicians as an outcome.

Three outcomes related to OCS use made it past the second round of voting and were discussed at the consensus meeting: continuous OCS use (>30 days), OCS use (>1 week), and OCS burst (≤ 1 week). The group agreed that bursts are likely captured by severe exacerbations, which already had strong support to be retained as a core outcome. Outside of therapy for exacerbations, it was important to have an outcome that captured overall corticosteroid exposure given that both individual corticosteroid prescriptions and total dose exposure are associated with AEs.^{36,37} Therefore, a new outcome, “number of days on systemic/oral corticosteroids,” was proposed to capture overall OCS exposure – particularly for those who oscillate between being on and off maintenance OCS therapy. We acknowledge this outcome does not incorporate dosage (e.g. days on 5 mg and 40 mg are counted equally). However, capturing both dosage and duration may prove too onerous and infeasible for incorporation into every clinical trial, contradicting the intended use of a COS. While this new outcome did not meet criteria to for inclusion in the final COS, 75% of patients voted it to be critical for inclusion. Change in rescue inhaler use and therapy step-down were also included as outcomes and made it to the final round of voting.

Four additional outcomes were rated as critically important by patients in Round 3 but did not meet inclusion criteria for the final COS: continuous OCS use (>30 days), asthma-specific ICU admission, moderate asthma exacerbation, and ability to perform daily tasks and household chores. While these outcomes were not included in the COS, their importance to patients warrants consideration in trial planning and longitudinal data collection. Consensus meeting discussions suggested certain functional outcomes can be folded into asthma-related QoL measures. Patients expressed “ability to perform daily tasks and household chores” underpinned other QoL metrics of psychological, emotional, and social effects of asthma. The importance of this outcome to patients was exemplified by the fact that 77% of patients compared to 35% of other voting members deemed it critically important in Round 3 voting.

While our process was methodologically robust, there are potential limitations that merit discussion. Most limitations are intrinsic to Delphi methodology which, although systematic in its approach, is reflective of voting and potentially biased by the consensus definitions³⁸ and voting panelists. Previous reviews showed that the reporting quality and the consensus methods used in medical research varies greatly and could lead to a lack of scientific credibility for adoption in practice.³⁸ We sought to mitigate these inherent methodological limitations commensurate with contemporary approaches and followed the practice guideline provided by Boukdedid et al. for planning and reporting the Delphi process^{9,16}: we utilized a priori defined methodology and consensus definitions, selected a heterogeneous panel member with diverse expertise to reflect the full range of relevant stakeholders, recruited voters from different countries, maintained separation of advisory committee and Delphi voting panel, provided feedback between rounds including qualitative comments and quantitative results, and analyzed and presented aggregated survey results anonymously. Although we sought to further minimize bias with a diverse stakeholder panel across disciplines, which importantly included patients, we acknowledge that a potential for selection bias of voting participants remains. For example, the patients participating were active in advocacy networks and may not be representative of the

broader population of asthma patients. Furthermore, patients particularly invested in the future of novel therapies may be more likely to participate or be interviewed during the background research stage. Also, our Delphi Panel only had two regulators. Nonetheless, by maintaining a balanced multi-stakeholder group across different decision-making entities including those involved in post-regulatory decision-making, we developed a COS that shows the effectiveness and value of novel therapies while remaining acceptable, in general, to patients who must endure the trials and disease. Our intent was to create a COS for moderate-to-severe asthma trials for global use, but heterogeneity of health care systems renders the relevance of particular healthcare resource utilization outcomes country-specific. Although our panel had international representation, the participants were predominantly from the US (63%), followed by Europe (29%), Canada (6%), and Singapore/Australia (2%). Hence, the COS should be adapted to different healthcare settings accordingly.

Critically, our final COS was intended to identify outcomes that should be measured, i.e. "what" to measure, without consideration of "how" to measure them. This challenge was previously highlighted in workshops regarding variable definitions of exacerbations and composite scores.^{22,39} During our consensus meeting, discussions of asthma control and QoL quickly pinpointed current measures of asthma QoL are not considered to accurately capture the patient experience. This feedback is consistent with a past review highlighting most QoL measures actually reflect asthma control, prompting the need for an instrument that provides a distinct, reliable measure of the patient's perception of the impact of asthma.⁴⁰ Therefore, next steps should focus on patient prioritization of QoL domains, guidance to improve asthma-specific QoL assessment, and ultimately, development of a publicly available, content-validated PRO measure for moderate-to-severe asthma. Additionally, our COS denotes that these outcomes are important but additional work is needed to identify what a minimally important clinical difference is.

These five outcomes represent a minimum set of outcomes that are relevant for use in phase 3 and phase 4 clinical drug trials in moderate-to-severe asthma. In the absence of the gold standard of single trials comparing multiple interventions, consistently collected, this COS will allow for comparisons across clinical trials of the effect of asthma therapies on symptoms, lung function, costs, and the daily lives of patients. Next steps should focus on standardizing on how to measure these outcomes. Following this, we encourage product developers and researchers to implement this recommended COS when developing study protocols for future clinical trials in moderate-to-severe asthma, as well as regulators, payers, and health technology assessors when evaluating drug therapies.

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Figure 1. Modified Delphi process used to reach consensus on a final COS

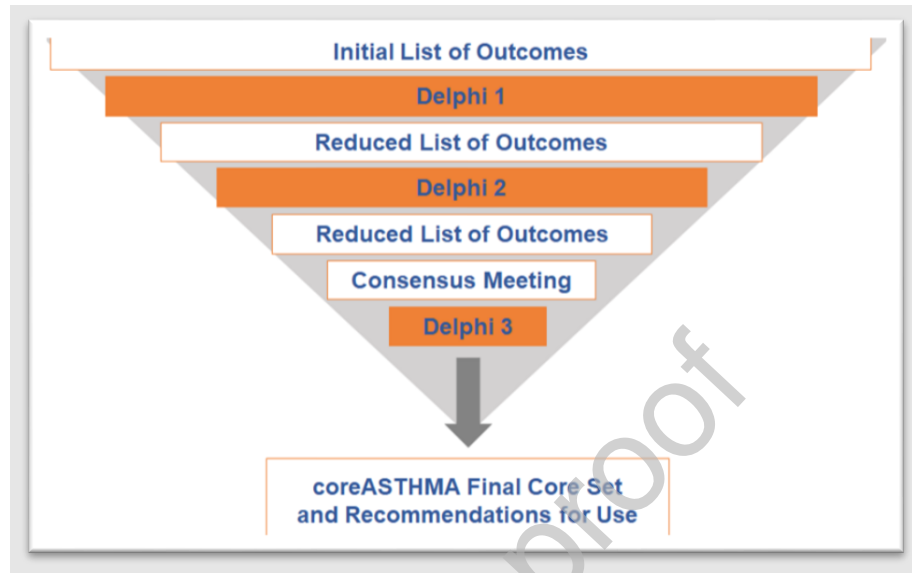


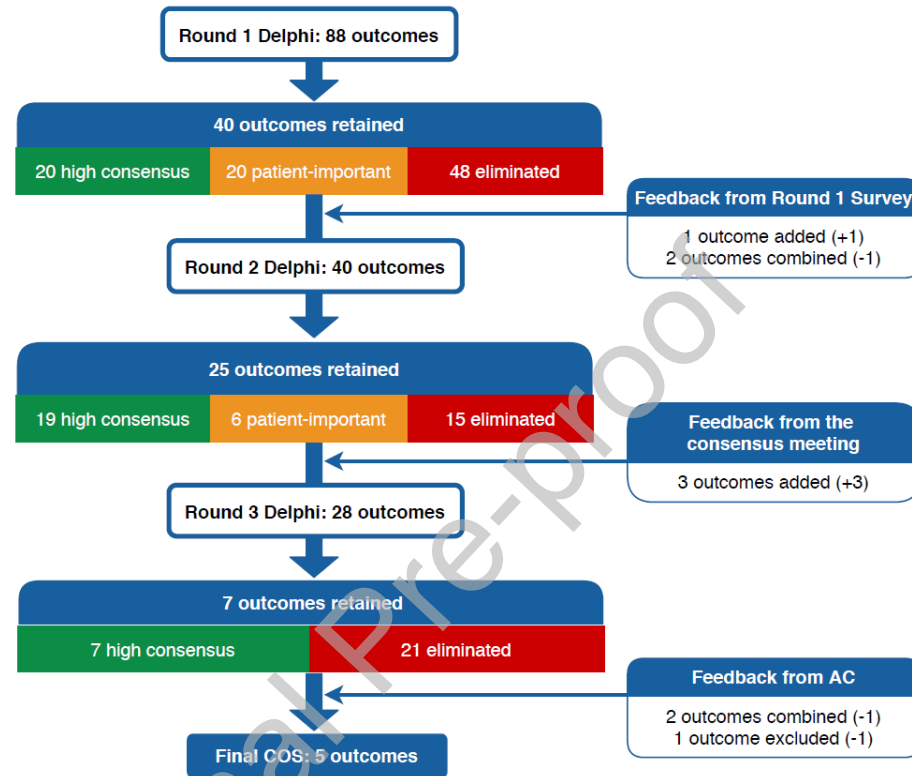
Figure 2. coreASTHMA Delphi Summary

Table 1. coreASTHMA Delphi Stakeholder Group Summary

Stakeholder Group	Number of Voters	% of Total Voters
Patients and Patient Advocates	13	28.8
Clinicians and Researchers	12	26.7
Life Science Companies*	10	22.2
Payers and HTA	8	17.8
Regulators	2	4.4

*5 of 10 involved in clinical development

Table 2. Levels of Importance of outcomes (on a scale of 1-9)

1-3	The outcome should not be included in the core outcome set
4-6	The outcome is important, but not critical to include in the core outcome set
7-9	The outcome is critical to include in the core outcome set

Table 3. coreASTHMA Consensus Definitions

Consensus to Select (high consensus)	An outcome in which $\geq 70\%$ of all voters rated the outcome with a score of 7, 8, or 9 ("critical importance")
Consensus to Select (patient-important)	An outcome in which $< 70\%$ of all voters rated the outcome 7, 8 or 9, but $\geq 70\%$ of voters in the Patient group rated the outcome with a score of 7, 8, or 9
Consensus to Eliminate	An outcome in which $< 70\%$ of voters rated the outcome 7, 8, or 9, AND $< 70\%$ of voters in the Patient group rated the outcome 7, 8 or 9

Table 4. coreASTHMA Summary of Changes to the Outcomes List

Source	Outcomes	Modifications	Rationale
Delphi Round 1 Comments	Adherence to controller therapy	Added to Resource Use outcomes	Voter suggestion
	Chest tightness	Expanded to include “chest pain”	May be used interchangeably
	- Asthma-specific quality of life - Severe asthma-specific quality of life	Combined	Overlap in intent
	Therapy step-up	Adjusted to include “increase/escalation in therapy”	Clarify definition
	Therapy step-down	Adjusted to include “reduction in therapy”	Clarify definition
Consensus Meeting Discussions	Asthma-specific hospital stay	Added to Resource Use outcomes	Capture being in a hospital bed in any setting for ≥ 24 hours due to asthma
	Number of days on systemic/oral corticosteroids	Added to Resource Use outcomes	Capture cumulative oral corticosteroid (OCS) exposure
	Reduction of OCS use	Added to Resource Use outcomes	Capture any reduction of OCS exposure
	Missed work days due to asthma	Adjusted to include “patient or caregiver”	Clarify definition
	Chest pain or tightness	Modified to “chest tightness or pain”	Clarify definition

Table 5. CoreASTHMA Final Core Outcome Set with Definition

	Outcome	Definition
Core Outcome Set	Severe Asthma Exacerbation	Severe asthma exacerbations are events that require urgent action on the part of the patient and clinician to prevent a serious adverse outcome, such as hospitalization or death from asthma. The occurrence of severe asthma exacerbations should be used as a marker of poor asthma control. The definition should include at least 1 of the following: (a) Use of oral systemic corticosteroids or an increase from a stable maintenance dose, for at least 3 days. For consistency, courses of corticosteroids separated by 1 week or more should be treated as separate severe exacerbations. A corticosteroid injection is also considered a discrete use of systemic corticosteroids. (b) A hospitalization or emergency department visit because of asthma, requiring systemic corticosteroids.
	Change in Asthma Control	Change in the extent to which the various manifestations of asthma are reduced or removed by treatment. There are currently several different tools (e.g. ACT, ACQ, ATAQ) available to measure and describe asthma control. Some are reported as a single summary score, others can be reported as a summary and by domain (e.g. change in symptom severity, quick-relief medication use, effect of asthma on everyday functioning, activity limitations, missed work or school, self-perception of asthma control, FEV1 prebronchodilator).
	Asthma-specific (or severe asthma-specific) Quality of Life	Similar concept to general health-related Quality of Life but tailored specifically to asthma patients ranging from mild to severe. There are several different tools available to measure asthma-specific Quality of Life, such as: Asthma Bother Profile (ABP), Asthma Index Survey (AIS-6), Asthma Quality of Life Questionnaire-Standardized (AQLQ-S), Mini Asthma Quality of Life Questionnaire (Mini-AQLQ), Living With Asthma Questionnaire (LWAQ), Modified Asthma Quality of Life Questionnaire-Marks (Modified AQLQ-Marks), St George's Respiratory Questionnaire (SGRQ), Airways Questionnaire-20. There are also tools available to measure severe asthma-specific Quality of Life, such as the Severe Asthma Questionnaire (SAQ). These all generate summary scores based on multiple components. For example, the Mini-AQLQ covers asthma symptoms, activities, emotions and environment.
	Asthma-specific Hospital Stay or Admission	Being in a hospital bed, in any setting (inpatient, ICU, emergency), for 24 hours or longer, or being admitted regardless of the duration due to asthma.
	Asthma-specific Emergency Department Visit	The number of emergency department visit due to asthma.
Adverse Event	Asthma-related Death	Death from asthma.

Supplementary Figures and Tables

eFigure 1 – Example of individual and summary reports given to participants prior to rounds 2 and 3 of Delphi voting

coreASTHMA Delphi Round 2 Retained Outcomes

Indicates that your response is 2 or more points higher or lower than the average of all voters.

Participant Name:	Your Response	All Voters	Patients/ Advocates	Clinicians/ Researchers	HTA/Payers	Regulators	Industry
PHYSIOLOGICAL / CLINICAL							
Moderate asthma exacerbation	9	7.4	7.6	7.1	6.8	6.5	8.2
Severe asthma exacerbation	9	8.5	8.6	8.8	8.0	8.0	8.5
Change in asthma control	9	7.8	7.5	7.5	7.5	8.5	8.5
Chest pain or tightness	5	5.8	7.1	4.8	5.0	6.0	6.1
Pre-bronchodilator lung function	8	7.2	8.0	6.3	6.9	7.5	7.7
Post-bronchodilator lung function	4	7.1	8.1	7.0	6.9	6.0	6.7
Forced expiratory volume one second/Forced vital capacity (FEV1/FVC) ratio	6	6.9	7.8	6.8	6.1	8.0	6.6
FUNCTIONING							
Asthma-specific (or severe asthma-specific) Quality of Life	6	7.9	7.9	7.7	7.9	8.0	8.1
Physical functioning (overall)	6	6.4	7.0	6.1	6.4	6.0	6.2
Ability to perform daily tasks and household chores	8	6.6	7.2	6.5	6.1	6.0	6.5
RESOURCE USE							
Missed work days due to asthma	5	7.2	7.8	7.1	7.0	5.5	7.3
Missed school days due to asthma	5	7.3	7.5	7.4	7.0	5.5	7.3
Lost earnings, earning capacity due to asthma	3	6.1	7.1	5.7	6.4	6.0	5.3
Asthma-specific hospital admissions	6	8.0	8.0	8.3	7.8	8.0	8.0
Asthma-specific ICU admissions	6	7.6	8.2	7.5	6.6	7.5	8.0
Therapy step-up (increase or escalation in treatment)	7	7.3	6.9	7.6	7.0	7.5	7.7
Therapy step-down (reduction in treatment)	3	7.2	6.9	7.6	7.3	7.5	7.0
Asthma-specific ED visits	7	7.8	8.0	8.5	6.5	8.0	7.9

eTable 1 – Initial 88 outcomes for voting mapped to COMET taxonomy

coreASTHMA Domains	COMET Categories (mapped list)
PHYSIOLOGICAL/CLINICAL (N=25)	
Moderate asthma exacerbation	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Severe asthma exacerbation	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Change in asthma control	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Symptom-free days per 30 days	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Shortness of breath or breathlessness	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Wheezing	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Chest tightness	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Frequency of daytime cough	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Frequency of nocturnal cough	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Mucus/phlegm (sputum)	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Sensitivity and tolerability to smell	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Pre-bronchodilator lung function	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Post-bronchodilator lung function	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Peak expiratory flow (PEF)	Physiological/clinical - Respiratory, thoracic and

	mediastinal outcomes
Forced expiratory volume one second/Forced vital capacity (FEV1/FVC) ratio	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Residual volume (RV)	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Total lung capacity (TLC)	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Airway hyperresponsiveness	Physiological/clinical - Respiratory, thoracic and mediastinal outcomes
Fatigue	Physiological/clinical - General Outcomes
Weight loss	Physiological/clinical - General Outcomes
Mental health (overall)	Physiological/clinical - Psychiatric Outcomes
Anxiety	Physiological/clinical - Psychiatric Outcomes
Depression	Physiological/clinical - Psychiatric Outcomes
Dizziness	Physiological/clinical - Nervous system outcomes
Sleep disturbance or night-time awakening	Functioning - Physical Functioning
FUNCTIONING (N=34)	
General health-related Quality of Life	Functioning - Global Quality of Life
Asthma-specific Quality of Life	Functioning - Global Quality of Life
Severe asthma-specific Quality of Life	Functioning - Global Quality of Life
Physical functioning (overall)	Functioning - Physical Functioning
Exercise tolerance	Functioning - Physical Functioning
Sexual functioning	Functioning - Physical Functioning
Ability to perform daily tasks and household chores	Functioning - Physical Functioning
Independence at home	Functioning - Physical Functioning
Ability to lift heavy objects	Functioning - Physical Functioning
Ability to do stairs	Functioning - Physical

	Functioning
Ability to travel	Functioning - Physical Functioning
Problems with eating	Functioning - Physical Functioning
Inability to speak (or laugh/cry)	Functioning - Physical Functioning
Tolerance of cold air	Functioning - Personal circumstances
Ability to participate in outdoor activities	Functioning - Personal circumstances
Ability to participate in active recreation	Functioning - Social functioning
Ability to participate in leisure activities	Functioning - Social functioning
Social well-being (overall)	Functioning - Social functioning
Relationship with family	Functioning - Social functioning
Relationship with close friends	Functioning - Social functioning
Relationship with spouse or partner	Functioning - Social functioning
Ability to perform child-rearing activities	Functioning - Role functioning
Work performance	Functioning - Role functioning
Ability to accomplish personal objectives	Functioning - Emotional functioning/well-being
Emotional well-being (overall)	Functioning - Emotional functioning/well-being
Mood changes	Functioning - Emotional functioning/well-being
Sadness	Functioning - Emotional functioning/well-being
Fear	Functioning - Emotional functioning/well-being
Self-worth	Functioning - Emotional functioning/well-being
Embarrassment	Functioning - Emotional functioning/well-being
Worry of long-term side effects	Functioning - Emotional functioning/well-being
Loneliness or isolation	Functioning - Emotional functioning/well-being
Optimism	Functioning - Emotional functioning/well-being

Negative coping behavior	Functioning - Emotional functioning/well-being
RESOURCE USE (N=27)	
Missed work days due to asthma	Resource use - Economic
Missed school days due to asthma	Resource use - Economic
Interrupted work days due to asthma	Resource use - Economic
Interrupted school days due to asthma	Resource use - Economic
Presenteeism	Resource use - Economic
Out-of-pocket asthma-specific ED visit costs	Resource use - Economic
Out-of-pocket asthma-specific hospitalization costs	Resource use - Economic
Out-of-pocket asthma-specific office visit costs	Resource use - Economic
Out-of-pocket asthma-specific medication costs	Resource use - Economic
Lost earnings, earning capacity due to asthma	Resource use - Economic
Financial burden due to asthma	Resource use - Economic
Non-medical indirect expenses due to asthma	Resource use - Economic
Transportation costs and time due to asthma	Resource use - Economic
Asthma-specific hospital admissions	Resource use - Hospital
Asthma-specific length of hospital stay	Resource use - Hospital
Asthma-specific ICU admissions	Resource use - Hospital
Asthma-specific ED visits	Resource use - Hospital
Asthma-specific unscheduled visits to a health facility	Resource use - Hospital
Asthma-specific outpatient visits	Resource use - Hospital
Asthma-specific remote visits	Resource use - Hospital
Change in rescue inhaler use	Resource use - Need for further intervention
Oral corticosteroid use (>1 week)	Resource use - Need for further intervention
Continuous OCS use (>30 days)	Resource use - Need for further intervention
Oral corticosteroids (OCS)	Resource use - Need for

burst (≤ 1 week)	further intervention
Therapy step-up	Resource use - Need for further intervention
Therapy step-down	Resource use - Need for further intervention
Caregiver burden due to asthma	Resource use - Societal/carer burden
MORTALITY/SURVIVAL (N=2)	
All-cause survival/mortality	Mortality/survival
Asthma-related death	Mortality/survival

eTable 2 – Detailed voting results from Delphi Round 1

		Percentage of Panel by Voting Category			Average Rating by Stakeholder Group					
		1-3	4-6	7-9	All Voters (N=43)	Patients/ Advocates (N=12)	Clinicians/ Researchers (N=12)	HTA/ Payers (N=7)	Regulators (N=2)	Industry (N=10)
		<i>PHYSIOLOGICAL / CLINICAL OUTCOMES</i>								
Retained	Moderate asthma exacerbation	0%	28%	72%	7.3	7.3	7.2	6.6	7.5	7.9
	Severe asthma exacerbation	2%	5%	93%	8.2	7.9	9.0	7.7	8.5	7.9
	Change in asthma control	2%	21%	76%	7.4	7.8	7.4	6.9	7.0	7.4
	Pre-bronchodilator lung function	2%	23%	74%	7.2	7.8	6.9	6.4	7.5	7.2
Retained: Patient- Important	Wheezing	5%	42%	53%	6.5	7.6	6.0	5.3	5.5	6.9
	Chest tightness	5%	51%	44%	6.4	7.7	5.8	5.1	5.5	6.5
	Post-bronchodilator lung function	5%	28%	67%	7.0	7.8	7.0	6.4	6.0	6.4
	Forced expiratory volume one second or Forced vital capacity (FEV1 to FVC) ratio	14%	24%	62%	6.7	7.4	6.3	6.6	7.5	6.5
	Mental health (overall)	16%	30%	53%	5.8	6.2	5.9	6.1	3.0	5.6
Eliminated	Symptom-free days per 30 days	14%	40%	47%	6.1	6.0	5.7	5.4	7.0	7.1
	Shortness of breath or breathlessness	2%	35%	63%	7.0	7.3	6.7	5.9	6.5	7.8
	Frequency of daytime cough	9%	58%	33%	5.8	6.7	5.7	5.0	4.0	5.9
	Frequency of nocturnal cough	12%	49%	40%	6.2	6.8	6.0	5.6	4.0	6.4

		Percentage of Panel by Voting Category				Average Rating by Stakeholder Group				
		1-3	4-6	7-9	All Voters (N=43)	Patients/ Advocates (N=12)	Clinicians/ Researchers (N=12)	HTA/ Payers (N=7)	Regulators (N=2)	Industry (N=10)
	Mucus or phlegm (sputum)	21%	47%	33%	5.5	6.8	4.8	4.4	5.5	5.4
	Sensitivity and tolerability to smell	62%	26%	12%	3.8	4.2	3.2	4.0	2.0	3.9
	Sleep disturbance or night-time awakening	5%	35%	60%	6.9	6.9	7.2	5.4	6.0	7.6
	Peak expiratory flow (PEF)	19%	33%	48%	6.0	6.0	5.2	6.3	6.0	6.8
	Residual volume (RV)	30%	40%	30%	5.1	6.1	4.3	5.3	4.0	5.0
	Total lung capacity (TLC)	34%	32%	34%	5.1	6.3	3.9	5.1	1.0	5.5
	Airway hyperresponsiveness	12%	41%	46%	5.9	6.2	6.2	5.6	2.5	6.0
	Fatigue	21%	43%	36%	5.5	5.3	5.7	5.3	3.5	6.2
	Weight loss	47%	44%	9%	3.8	4.3	3.5	4.4	2.5	3.4
	Dizziness	45%	38%	17%	3.9	4.5	3.3	5.0	2.5	3.3
	Anxiety	9%	51%	40%	5.8	6.4	5.8	5.4	3.0	5.8
	Depression	14%	49%	37%	5.7	6.2	5.8	5.4	3.0	5.5
FUNCTIONING OUTCOMES										
Retained	Asthma-specific quality of life	0%	9%	91%	7.8	8.3	7.7	7.7	7.0	7.6
	Severe asthma - specific quality of life	5%	16%	79%	7.3	8.5	7.7	6.4	6.0	6.5
Retained: Patient-Important	Physical functioning (overall)	5%	33%	62%	6.9	8.1	6.8	6.6	3.0	6.6
	Ability to perform daily tasks and household chores	12%	33%	56%	6.3	7.7	5.9	5.6	3.0	6.2

		Percentage of Panel by Voting Category				Average Rating by Stakeholder Group				
		1-3	4-6	7-9	All Voters (N=43)	Patients/ Advocates (N=12)	Clinicians/ Researchers (N=12)	HTA/ Payers (N=7)	Regulators (N=2)	Industry (N=10)
	Ability to participate in active recreation	9%	47%	44%	6.2	7.3	6.0	5.3	3.0	6.2
	Ability to accomplish personal objectives	10%	51%	39%	5.7	7.1	6.0	5.1	4.0	4.8
	Ability to do stairs	14%	42%	44%	5.8	7.2	5.3	5.6	4.5	5.1
	Ability to travel	26%	45%	29%	5.0	7.2	4.3	5.1	3.0	3.8
	Inability to speak (or laugh or cry)	31%	26%	43%	5.5	6.9	4.9	5.4	5.0	4.6
	Tolerance of cold air	19%	45%	36%	5.3	7.0	4.9	4.1	5.0	4.5
	Social well-being (overall)	10%	38%	52%	6.0	7.1	5.4	6.4	3.0	5.8
	Worry of long-term side effects	7%	43%	50%	6.5	7.4	7.1	5.4	4.0	6.3
<i>Eliminated</i>	General health-related quality of life	12%	45%	43%	5.9	6.8	5.9	6.3	2.0	5.5
	Exercise tolerance	2%	47%	51%	6.6	7.4	6.6	5.4	6.0	6.4
	Sexual functioning	39%	41%	20%	4.4	4.4	4.2	4.4	2.5	4.9
	Independence at home	19%	52%	29%	5.3	6.9	4.3	5.3	2.5	5.3
	Ability to participate in leisure activities	7%	56%	37%	6.0	7.2	6.0	5.0	3.0	5.8
	Ability to participate in outdoor activities	7%	59%	34%	5.9	6.7	5.7	5.3	4.0	5.8
	Ability to lift heavy objects	46%	39%	15%	4.1	5.3	4.3	3.9	2.0	3.1
	Problems with eating	33%	48%	19%	4.6	5.3	4.0	5.6	3.5	4.1
	Relationship with family	29%	52%	19%	4.7	5.7	4.7	4.9	2.5	3.8

		Percentage of Panel by Voting Category			Average Rating by Stakeholder Group					
		1-3	4-6	7-9	All Voters (N=43)	Patients/ Advocates (N=12)	Clinicians/ Researchers (N=12)	HTA/ Payers (N=7)	Regulators (N=2)	Industry (N=10)
	Relationship with close friends	43%	48%	10%	4.1	4.7	4.0	4.9	2.0	3.6
	Relationship with spouse or partner	39%	44%	17%	4.5	6.0	4.0	5.1	2.0	3.8
	Ability to perform child-rearing activities	22%	55%	22%	5.1	6.0	4.8	5.4	2.0	4.7
	Work performance	7%	45%	48%	6.0	6.5	6.7	5.9	3.5	5.4
	Emotional well-being (overall)	7%	41%	51%	6.3	7.2	5.8	6.6	5.0	5.9
	Mood changes	24%	60%	17%	4.7	5.6	4.6	4.7	3.5	4.0
	Sadness	26%	60%	14%	4.5	5.5	4.6	4.6	2.5	3.8
	Fear	17%	59%	24%	5.2	5.4	5.2	6.1	4.0	4.6
	Self-worth	24%	56%	20%	4.8	5.2	4.5	5.1	2.0	4.6
	Embarrassment	24%	56%	20%	4.8	4.9	4.9	5.3	2.0	4.6
	Loneliness or isolation	26%	60%	14%	4.8	5.1	4.8	4.9	3.0	4.7
	Optimism	33%	55%	12%	4.5	4.7	4.2	4.7	2.5	4.9
	Negative coping behavior	36%	52%	12%	4.5	4.5	4.5	5.4	2.5	4.3
RESOURCE USE OUTCOMES										
Retained	Missed work days due to asthma	0%	12%	88%	7.7	8.2	8.1	6.9	7.0	7.2
	Missed school days due to asthma	2%	9%	88%	7.7	7.8	8.2	6.9	7.0	7.4
	Asthma-specific hospital admissions	2%	2%	95%	8.0	8.2	8.4	7.9	8.5	7.3
	Asthma-specific length of hospital stay	5%	21%	74%	7.2	7.6	7.2	6.9	6.0	7.3

		Percentage of Panel by Voting Category			Average Rating by Stakeholder Group					
					All Voters (N=43)	Patients/ Advocates (N=12)	Clinicians/ Researchers (N=12)	HTA/ Payers (N=7)	Regulators (N=2)	Industry (N=10)
		1-3	4-6	7-9						
	Asthma-specific ICU admissions	0%	19%	81%	7.9	8.6	8.0	6.4	8.0	7.8
	Asthma-specific ED visits	0%	14%	86%	7.9	8.2	8.8	6.7	7.0	7.5
	Asthma-specific unscheduled visits to a health facility	7%	19%	74%	7.3	7.5	8.3	6.0	7.0	6.8
	Change in rescue inhaler use	0%	16%	84%	7.7	7.9	8.2	6.9	7.5	7.4
	Oral corticosteroid use (>1 week)	0%	16%	84%	8.0	8.2	8.5	6.7	8.0	8.0
	Continuous OCS use (> 30 days)	0%	14%	86%	8.0	8.3	8.2	7.1	8.0	8.0
	Oral corticosteroid use (≥1 week)	2%	23%	74%	7.5	7.0	8.8	6.0	6.5	7.8
	Therapy step-up	0%	21%	79%	7.4	7.8	7.2	6.7	6.5	7.7
	Therapy step-down	0%	23%	77%	7.3	7.8	7.2	6.9	6.5	7.6
Retained: Patient- Important	Out-of-pocket asthma-specific ED visit costs	10%	36%	54%	6.5	8.2	6.5	6.0	3.0	5.6
	Out-of-pocket asthma-specific hospitalization costs	10%	38%	51%	6.4	8.2	6.5	6.0	3.0	5.3
	Out-of-pocket asthma-specific office visit costs	10%	36%	54%	6.4	8.1	6.4	6.0	3.0	5.4
	Out-of-pocket asthma-specific medication costs	10%	36%	55%	6.6	8.3	6.8	5.9	3.0	5.3
	Lost earnings, earning	5%	35%	60%	6.7	7.6	6.2	6.3	6.5	6.5

		Percentage of Panel by Voting Category			Average Rating by Stakeholder Group					
		1-3	4-6	7-9	All Voters (N=43)	Patients/ Advocates (N=12)	Clinicians/ Researchers (N=12)	HTA/ Payers (N=7)	Regulators (N=2)	Industry (N=10)
		capacity due to asthma								
Eliminated	Interrupted work days due to asthma	5%	40%	56%	6.6	7.2	7.2	5.9	6.0	5.6
	Interrupted school days due to asthma	7%	37%	56%	6.5	6.8	7.2	5.9	6.0	5.9
	Presenteeism	10%	54%	37%	6.0	6.2	6.2	5.4	4.5	6.3
	Financial burden due to asthma	10%	33%	57%	6.6	7.4	6.8	6.1	4.0	5.8
	Non-medical indirect expenses due to asthma	17%	50%	33%	5.8	6.1	5.8	6.3	3.0	5.4
	Caregiver burden due to asthma	5%	33%	62%	6.5	7.2	6.8	6.4	4.0	6.2
	Transportation costs and time due to asthma	21%	56%	23%	5.3	6.2	5.2	5.0	2.5	
	Asthma-specific outpatient visits	12%	28%	60%	6.7	7.1	6.9	6.0	4.5	6.9
	Asthma-specific remote visits	18%	35%	48%	6.2	7.2	6.7	5.1	4.0	5.4
MORTALITY AND SURVIVAL OUTCOMES										
Retained	Asthma-related death	0%	14%	86%	8.3	8.9	8.3	7.9	8.5	7.8
Eliminated	All-cause survival or mortality	10%	39%	51%	6.8	6.7	7.4	6.4	7.0	6.4

eTable 3 – Detailed voting results from Delphi Round 2

		Percentage of Panel by Voting Category			Average Rating by Stakeholder Group					
		1-3	4-6	7-9	All Voters (N=43)	Patients/ Advocates (N=11)	Clinicians/ Researchers (N=12)	HTA/ Payers (N=8)	Regulators (N=2)	Industry (N=10)
<i>PHYSIOLOGICAL / CLINICAL OUTCOMES</i>										
Retained	Moderate asthma exacerbation	2%	23%	74%	7.4	7.6	7.1	6.8	6.5	8.2
	Severe asthma exacerbation	0%	0%	100%	8.5	8.6	8.8	8.0	8.0	8.5
	Change in asthma control	2%	7%	91%	7.8	7.5	7.5	7.5	8.5	8.5
	Pre-bronchodilator lung function	5%	21%	74%	7.2	8.0	6.3	6.9	7.5	7.7
Retained: Patient- Important	Chest pain or tightness	17%	52%	31%	5.8	7.1	4.8	5.0	6.0	6.1
	Post-bronchodilator lung function	2%	28%	70%	7.1	8.1	7.0	6.9	6.0	6.7
	Forced expiratory volume one second/Forced vital capacity (FEV1/FVC) ratio	5%	33%	62%	6.9	7.8	6.8	6.1	8.0	6.6
Eliminated	Wheezing	9%	56%	35%	6.1	7.0	5.1	5.2	5.0	7.3
	Mental health (overall)	16%	65%	19%	5.2	5.3	5.6	5.6	3.5	4.6
<i>FUNCTIONING OUTCOMES</i>										
Retained	Asthma-specific or severe asthma-specific Quality of Life	0%	7%	93%	7.9	7.9	7.7	7.9	8.0	8.1
Retained:	Physical functioning	5%	43%	52%	6.4	7.0	6.1	6.4	6.0	6.2

		Percentage of Panel by Voting Category				Average Rating by Stakeholder Group				
		1-3	4-6	7-9	All Voters (N=43)	Patients/ Advocates (N=11)	Clinicians/ Researchers (N=12)	HTA/ Payers (N=8)	Regulators (N=2)	Industry (N=10)
Patient- Important	(overall)									
	Ability to perform daily tasks and household chores	5%	43%	52%	6.6	7.2	6.5	6.1	6.0	6.5
Eliminated	Ability to participate in active recreation	10%	55%	36%	6.1	6.6	6.4	5.8	7.0	5.2
	Ability to accomplish personal objectives	7%	62%	31%	5.9	6.4	6.6	5.5	7.0	4.9
	Ability to do stairs	12%	51%	37%	6.0	6.6	5.4	5.9	5.5	6.1
	Ability to travel	19%	57%	24%	5.3	6.2	5.0	4.9	6.0	5.1
	Inability to speak (or laugh or cry)	19%	40%	40%	5.9	6.6	5.4	6.4	8.0	5.1
	Tolerance of cold air	26%	53%	21%	5.2	6.5	5.0	4.9	4.5	4.6
	Social well-being (overall)	19%	53%	28%	5.5	5.5	5.8	6.4	4.5	4.5
	Worry of long-term side effects	21%	49%	30%	5.4	5.6	6.3	5.4	4.5	4.2
RESOURCE USE OUTCOMES										
Retained	Missed work days due to asthma	0%	26%	74%	7.3	7.8	7.4	7.0	5.5	7.3
	Missed school days due to asthma	0%	28%	72%	7.3	7.5	7.4	7.0	5.5	7.3
	Asthma-specific hospital admissions	0%	7%	93%	8.0	8.0	8.2	7.8	8.0	8.0
	Asthma-specific ICU admissions	7%	12%	81%	7.6	8.2	7.5	6.6	7.5	8.0
	Therapy step-up	0%	24%	76%	7.3	6.9	7.6	7.0	7.5	7.7

		Percentage of Panel by Voting Category			Average Rating by Stakeholder Group					
		1-3	4-6	7-9	All Voters (N=43)	Patients/ Advocates (N=11)	Clinicians/ Researchers (N=12)	HTA/ Payers (N=8)	Regulators (N=2)	Industry (N=10)
	(increase or escalation in treatment)									
	Therapy step-down (reduction in treatment)	2%	27%	71%	7.2	6.9	7.6	7.2	7.5	7.0
	Asthma-specific ED visits	5%	0%	95%	7.8	8.0	8.5	6.5	8.0	7.9
	Asthma-specific unscheduled visits to a health facility	7%	17%	76%	7.3	7.6	8.1	5.8	8.0	7.3
	Change in rescue inhaler use	0%	24%	76%	7.4	7.2	7.8	6.4	7.5	7.9
	Oral corticosteroid use (more than 1 week)	0%	17%	83%	7.8	7.9	8.5	6.2	9.0	8.0
	Continuous OCS use (more than 30 days)	0%	10%	90%	7.8	8.2	7.9	6.6	9.0	8.0
	Oral corticosteroids (OCS) burst (less than or equal to 1 week)	0%	27%	73%	7.6	7.7	8.5	5.9	9.0	7.8
	Adherence to therapy	5%	18%	77%	6.9	7.6	7.7	6.5	7.0	5.8
Retained: Patient-Important	Lost earnings, earning capacity due to asthma	14%	43%	43%	6.1	7.1	5.7	6.4	6.0	5.3
Eliminated	Out-of-pocket asthma-specific ED	26%	40%	35%	5.6	6.6	5.7	5.2	1.5	5.3

		Percentage of Panel by Voting Category			Average Rating by Stakeholder Group					
		1-3	4-6	7-9	All Voters (N=43)	Patients/ Advocates (N=11)	Clinicians/ Researchers (N=12)	HTA/ Payers (N=8)	Regulators (N=2)	Industry (N=10)
	visit costs									
	Out-of-pocket asthma-specific hospitalization costs	23%	42%	35%	5.7	6.6	5.8	5.2	1.5	5.5
	Out-of-pocket asthma-specific office visit costs	23%	42%	35%	5.6	6.6	6.1	5.2	1.5	5.1
	Out-of-pocket asthma-specific medication costs	19%	47%	35%	5.8	6.7	6.4	5.2	1.5	5.3
	Asthma-specific length of hospital stay	7%	28%	65%	7.1	7.3	7.1	6.4	6.0	7.6
MORTALITY AND SURVIVAL OUTCOMES										
Retained	Asthma-related death	0%	21%	79%	7.7	8.7	7.9	7.9	6.0	6.5

eTable 4 – Detailed voting results from Delphi Round 3

OUTCOMES	Percentage Rating 7-9					
	All (N=44)	Patients/ Advocates (N=13)	Clinicians/ Researchers (N=12)	HTA/ Payers (N=7)	Regulators (N=2)	Industry (N=10)
RETAINED						
Severe asthma exacerbation	98%	100%	100%	86%	100%	100%
Asthma-specific (or severe asthma-specific) Quality of Life	89%	100%	92%	86%	50%	80%
Change in asthma control	84%	85%	83%	86%	50%	90%
Asthma-specific hospital stay	81%	92%	64%	86%	100%	80%
Asthma-specific hospital admissions	74%	92%	67%	43%	50%	90%
Asthma-related death	73%	77%	75%	71%	50%	70%
Asthma-specific ED visits	71%	77%	67%	57%	0%	89%
ELIMINATED						
Moderate asthma exacerbation	68%	85%	50%	43%	100%	80%
Number of days on systemic/oral corticosteroid	68%	75%	67%	57%	0%	78%
Asthma-specific ICU admissions	67%	85%	45%	43%	50%	90%
Pre-bronchodilator lung function	66%	62%	67%	43%	100%	80%
Asthma-specific unscheduled visits to a health facility	65%	69%	83%	29%	100%	60%
Change in rescue inhaler use	63%	69%	50%	57%	50%	78%
Therapy step-up (increase or escalation in treatment)	61%	62%	42%	71%	50%	80%
Physical functioning (overall)	59%	69%	50%	43%	0%	80%
Continuous OCS use (>30 days)	58%	92%	27%	43%	0%	70%
Missed work days (patient or caregiver) due to asthma	58%	62%	58%	43%	100%	60%
Oral corticosteroids (OCS) burst (≤ 1 week)	58%	69%	67%	0%	0%	80%
Reduction of OCS use	58%	69%	64%	29%	0%	70%
Adherence to therapy	57%	62%	58%	71%	0%	50%
Oral corticosteroid use (>1 week)	53%	69%	42%	43%	100%	50%
Therapy step-down (reduction in treatment)	52%	69%	33%	43%	50%	60%

Ability to perform daily tasks and household chores	49%	77%	25%	29%	0%	60%
Missed school days due to asthma	47%	54%	42%	43%	0%	50%
Post-bronchodilator lung function	41%	62%	42%	43%	0%	20%
Chest tightness or pain	36%	46%	8%	29%	50%	60%
Forced expiratory volume one second/Forced vital capacity (FEV1/FVC) ratio	30%	42%	17%	29%	50%	30%
Lost earnings, earning capacity, due to asthma	28%	54%	17%	14%	0%	20%