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Asthma Outcomes Workshop: Overview

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Abstract

Background—Asthma clinical research will highly benefit from standardization of major outcomes in terms of definition and assessment methodology. This will permit useful comparisons across interventional or observational studies and will allow more effective data sharing.

Objective—National Institutes of Health (NIH) institutes and the Agency for Healthcare Research and Quality (AHRQ) convened a workshop involving 7 expert subcommittees to propose which asthma outcomes should be assessed with standardized methodology in future asthma clinical research studies.

Methods—Each subcommittee utilized comprehensive literature reviews and expert opinion to compile a list of asthma outcomes, and classified them as either core (required in future studies), supplemental (to be used according to study aims and standardized), or emerging (requiring validation and standardization). This work was discussed at an NIH-organized workshop in March 2010 and finalized in September 2011.

Results—Outcomes for study participant characterization, as well as for prospective clinical trial intervention and observational studies, were proposed for adults and children, and methodologies for outcome collection and reporting were determined. Furthermore, the workshop identified areas in which new outcomes or instruments for their measurement need to be developed and validated.

Conclusions—Standardized outcomes for clinical research in asthma have been proposed. Participating NIH institutes and other federal agencies will consider these recommendations in future clinical research initiatives in asthma.

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Keywords

Asthma clinical research; NIH asthma initiatives; standardizing outcomes

Background

Asthma is a major public health problem that affects almost 25 million Americans.[1] Clinical research, including clinical trials,* in asthma is supported by various governmental and nongovernmental organizations, as well as the pharmaceutical industry. It is well recognized that clinical research in asthma will highly benefit from standardization of the major clinical outcomes in terms of definition and assessment methodology. Such standardization will permit useful comparisons across interventional or observational clinical studies, genome-wide association studies, and data sharing.

Objectives

An Asthma Outcomes workshop was convened in Bethesda, Md, on March 15 and 16, 2010, by a consortium of several National Institutes of Health (NIH) institutes and the Agency for Healthcare Research and Quality. The 2 key objectives of the workshop were (1) to establish standard definitions and data collection methodologies for validated outcome measures in asthma clinical research with the goal of enabling comparisons across asthma research studies and clinical trials and (2) to identify promising outcome measures for asthma clinical research and comment on their status and further validation needs.

The participating federal agencies will consider the recommendations of the workshop report to identify a selective set of outcomes that will be required outcome measures in agency-initiated asthma clinical research programs, including clinical trials, observational/cross-sectional studies, and genetic studies. This will accelerate the widespread use of the data produced by asthma clinical research by permitting meaningful comparative analyses and enhancing the level of confidence in the research findings. It also will help promote the translation of research into clinical practice and health policy.

This Asthma Outcomes workshop report, which consists of 7 individual articles, represents the recommendations of the workshop participants for core, supplemental, and emerging outcomes, as defined below, for 7 domains of asthma clinical research outcome measures: biomarkers, composite scores of asthma control, exacerbations, healthcare utilization and costs, pulmonary physiology, quality of life, and symptoms.

*NIH definition of *clinical research:*
Patient-oriented research, including epidemiologic and behavioral studies, outcomes research, and health services research. Patient-oriented research is research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) in which a researcher directly interacts with human subjects. It includes research on mechanisms of human disease, therapeutic interventions, clinical trials, and development of new technologies, but does not include *in vitro* studies using human tissues not linked to a living individual. Studies falling under 45 CFR 46.101(b) (4) are not considered clinical research for purposes of this definition.
NIH definition of *clinical trial:*
A biomedical or behavioral research study of human subjects designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective. (http://grants.nih.gov/grants/glossary.htm)

1. **Core** asthma outcome measures: a selective set of asthma outcomes to be considered as requirements in the funding of NIH-initiated asthma clinical trials and large observational studies. The criteria for identifying these outcomes were (1) inclusion of the most important clinical aspects of asthma, (2) evidence of the outcome's validity, and (3) potential for the standardization of the outcome to enable homogeneous meta-analyses across studies and promote translation of research into clinical practice and health policy. In addition, core outcomes need to be safely and easily obtained and affordable for clinical studies involving large numbers of participants. Core outcomes are not to be confused with the primary outcomes of a clinical study. Depending on study design, a core outcome also may play a primary outcome role; however, the purpose of core outcomes is to allow for cross-study harmonization, as described above, whether the outcomes of interest are related to primary or secondary research aims.
2. **Supplemental** asthma outcome measures: asthma outcomes for which standard definitions can or have been developed, methods for measurement can be specified, and validity has been proven, but whose inclusion in funded clinical asthma research will be optional. Such outcomes may only apply to some forms of clinical research or may be too cumbersome or expensive for inclusion in all studies.
3. **Emerging** asthma outcome measures: asthma outcomes that have the potential (1) to expand and/or improve current aspects of disease monitoring and (2) to improve translation of basic and animal model-based asthma research into clinical research. Emerging asthma outcomes may be new or may have been previously used in asthma clinical research, but are not yet standardized and require further development and validation.

The responsibility for the workshop report and recommendations is solely that of the Planning Committee and subcommittee members. The workshop report is not an official document of any government agency.

Members of the Workshop

The Asthma Outcomes workshop was organized by a consortium of governmental and nongovernmental organizations, including the National Institute of Allergy and Infectious Diseases (NIAID), the National Heart, Lung, and Blood Institute (NHLBI), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Institute of Environmental Health Sciences (NIEHS), the Agency for Healthcare Research and Quality (AHRQ) and the Merck Childhood Asthma Network. Representatives of the above organizations formed a Planning Committee that had the overall responsibility for the workshop.

The Planning Committee selected the workshop co-chairs and invited 79 asthma researchers to serve on subcommittees reflecting 7 domains of asthma outcomes, as described above. The Planning Committee also selected 2 co-chairs for each subcommittee. Recognizing the various perspectives that might influence the selection of outcome measures, the Planning Committee ensured that each subcommittee had representatives from the specialties of adult

asthma, pediatric asthma, pulmonology, and allergy/immunology. Further, representatives from the fields of pharmacology, biostatistics, primary care, and behavioral/social science were included in the subcommittee membership.

The co-chairs of each subcommittee and the Planning Committee members served as the Executive Committee (EC) to organize development of the workshop report and meeting discussions, and review and approve the final workshop report. To contribute to the evaluation of the subcommittees' draft reports during the March 2010 workshop discussions, the EC invited 2 additional groups: (1) discussants to present critiques of the subcommittee reports at the workshop, from either the perspective of an asthma clinical researcher or an end-user of research findings, such as groups involved in quality improvement, guidelines development, or health policy, and (2) representatives from other federal agencies with asthma programs, the pharmaceutical industry, healthcare policy groups, and lay voluntary organizations. A list of workshop participants, denoting co-chairs, Planning Committee members, subcommittee members, discussants, and participant observers is presented in Table I. All comments by non-subcommittee participants at the workshop were considered, but the responsibility for the workshop report and recommendations is solely that of the Planning Committee and subcommittee members.

Development of the Workshop Report

The workshop report is comprised of 7 individual articles, 1 from each subcommittee. Each subcommittee met through frequent telephone conference calls and e-mail exchanges over the course of 9 months to prepare a draft report on its respective topic. The subcommittees were responsible for defining the scope of their topic, conducting appropriate literature reviews, drafting their report and recommendations for discussion by all workshop participants, and revising their report following the workshop. Through a contract funded by contributions of the Planning Committee participant organizations, RAND Health of the RAND Corporation conducted 1 systematic review of the literature for each subcommittee, according to the respective subcommittee's request. The literature was from peer-reviewed scientific publications in the English language published through March 2010.

Each subcommittee also discussed the relevant section of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Statement: Asthma Control and Exacerbations —Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice[2] (hereafter referred to as the *ATS/ERS Statement*) at the beginning of its work. Subcommittees built upon the *ATS/ERS Statement* as much as possible to develop their recommendations as to core, supplemental, and emerging asthma outcomes for future NIH research.

The EC met through monthly telephone conference calls to provide overall direction and coordination to the subcommittees, provide general templates for the preparation of each subcommittee's report, help ensure consistency, and organize the workshop meeting. At the workshop, each subcommittee's draft report was discussed at length by all workshop participants. After the workshop, the subcommittees revised their reports and produced the articles of this journal supplement. The EC met by telephone conference call to review and approve each subcommittee's final recommendations.

Support

Contributions from the organizations represented on the Planning Committee and a grant from the Robert Wood Johnson Foundation provided all funds for the literature searches, travel, lodging, and conference logistics for workshop co-chairs Drs Busse and Morgan, subcommittee members, and discussants. All other meeting participants travelled at their own expense. Contributions from NHLBI, NIAID, NICHD, NIEHS, and the US Environmental Protection Agency provided support for publication of the workshop report.

Additional Considerations

Mediators of asthma outcomes

The Quality of Life Subcommittee recognized that such factors as patient adherence, level of asthma self-management skills, and exposure to stress can have considerable influence on a wide range of asthma outcomes, not just the patients' perceptions of the impact of asthma on their quality of life. Although the review of these mediators was beyond the scope of any 1 subcommittee's topic, the Quality of Life Subcommittee offers a brief summary of these factors and their potential influence to encourage consideration of these issues in a broad range of asthma clinical research. This summary is presented as an additional article in the workshop report.

Validation studies of questionnaires or interview instruments

The Composite Scores of Asthma Control, Quality of Life, and Symptoms Subcommittees reviewed the psychometric properties of a variety of instruments identified through their literature searches. These reviews revealed considerable variation in how investigators defined the terms of construct, convergent, and criterion in presenting evidence concerning the validity of their instruments. Therefore, it was not possible to expect each subcommittee to use uniform definitions, such as those contained in the standards for educational and psychological testing issued jointly by the American Educational Research Association, American Psychological Association, and National Council on Measurement in Education.[3] As noted by the authors, these standards apply not only to measurement instruments commonly considered "tests," but also to scales, inventories, and any other evaluative procedure in which a sample of an examinee's behavior is obtained and subsequently evaluated and scored using a standardized process. Consequently, each subcommittee's article contains the definitions used. This issue underscores yet another dimension of standardization that is needed for the development of asthma outcome measures. Developers of future asthma outcome instruments that depend on patient report or performance are encouraged to utilize these published, widely accepted standards, in much the same manner as the asthma community utilizes the ATS standards for lung function measurements.

Demographic characterization

Each article of the workshop report includes a recommendation for the demographic characterization of the study population, noting that such features as age, sex, race or ethnicity, and socioeconomic status may influence measurement or interpretation of outcomes of interest to the subcommittee. However, there is an overarching need for basic

demographic characterization of the population to also use standardized definitions. For example, the differentiation of age groups 0-4 years, 5-11 years, and ≥12 years is common among asthma studies and clinical practice guidelines. However, the Exacerbations Subcommittee notes a need to distinguish adolescents (ages 12-17 years), adults 18-64, and older adults 65 and older. It is apparent from the literature reviewed that investigators have used varying categorizations of race and ethnicity as well as socioeconomic status. Future investigators are encouraged, at a minimum, to report the specific definitions they use, and are further encouraged to use the NIH's standard definitions of race and ethnicity (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html) and a referenced source for defining socioeconomic status (eg, the proportion of the study population below the poverty level as defined by the US Census Bureau, http://www.census.gov/hhes/www/poverty/methods/definitions.html, or the level of education of study participants or their households).

Patient-reported outcomes

The Patient Report Outcomes Measurement System (PROMIS) is a trans-NIH initiative, managed by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, to develop new, standardized, and psychometrically robust ways to measure patient-reported symptoms such as pain, fatigue, physical functioning, and aspects of health-related quality of life across a wide variety of chronic diseases and conditions (http://nihroadmap.nih.gov/clinicalresearch/promis). The goal is to develop a set of publicly available computerized adaptive tests for the clinical research community. Researchers will select from a bank of questionnaire items related to different domains (eg, pain, fatigue) to create questionnaires for their respective studies, whether administered through an iterative computer adaptive testing system or paper version short forms. PROMIS is now testing the application of its initial generic domains for use in patients with specific diseases, including asthma. Because this initiative is still in development, the Asthma Outcomes workshop could not conduct a review of PROMIS instruments. However, it is hoped that this brief description will encourage clinical investigators to check the PROMIS Web site for updates that may be helpful for their research.

Summary

The enthusiasm with which such a large cross-section of clinical research scientists in asthma worked together to develop proposals for standardizing asthma outcomes reflects the high level importance of this endeavor. Workshop participants endorsed the conviction that harmonization of asthma outcomes is critical for cross-study comparisons, genome-wide association studies, and data sharing. It is hoped that investigators in the medical and scientific communities will incorporate these workshop proposals into their future research and will undertake research to further enhance asthma outcomes measurement.

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Abbreviations

ABP	Asthma Bother Profile
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AHRQ	Agency for Healthcare Research and Quality
AIS-6	Asthma Index Survey
AQ-20	Airways Questionnaire-20
AQLQ-S	Asthma Quality of Life Questionnaire-Standardized
ASS	Asthma Severity Score
ASUI	Asthma Symptom Utility Index
ATAQ	Asthma Therapy Assessment Questionnaire
ATS	American Thoracic Society
cACT	Childhood Asthma Control Test
CAS	Clinical Asthma Score
CBC	Complete blood count
CHSA	Child Health Survey for Asthma
EC	Executive Committee
ED	Emergency department
ERS	European Respiratory Society
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
ICU	Intensive care unit
LTE_4	Leukotriene E4
LWAQ	Living With Asthma Questionnaire
Mini-AQLQ	Mini Asthma Quality of Life Questionnaire
Modified AQLQ-Marks	Modified Asthma Quality of Life Questionnaire-Marks
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases

NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
PACD	Pediatric Asthma Caregiver Diary
PAQLQ	Pediatric Asthma Quality of Life Questionnaire
PASS	Pediatric Asthma Severity Score
Pediatric Caregiver AQLQ	Pediatric Caregiver Asthma Quality of Life Questionnaire
PedsQL	Pediatric Quality of Life Inventory
PEF	Peak expiratory flow
PI	Pulmonary Index
PRAM	Preschool Respiratory Assessment Measure
PROMIS	Patient Report Outcomes Measurement System
PS	Pulmonary Score
SES	Socioeconomic status
SGRQ	St George's Respiratory Questionnaire
UC	Urgent care
WPAI	Work Productivity and Activity Impairment Questionnaire

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Key Recommendations

- A summary of the key workshop proposals for core and supplemental measures are presented in Tables II-V. Each subcommittee's individual article provides discussion and references to the scientific literature that support these recommendations.
- In some instances, the subcommittees were unable to identify core outcomes. This reflected either the lack of adequate validation and standardization or the opinion of subcommittee members that the content of an existing tool may not adequately represent the essence of the outcome for which it was developed. In these cases, the subcommittees have identified clear needs for the development and validation of new tools.
- For outcomes and outcome measures that, despite their potential importance, have been designated as emerging because of the lack of adequate validation and standardization, the articles of the workshop report raise specific questions that need to be addressed in future research.
- Each subcommittee presents suggestions for future directions and research to help guide future projects that could fill existing gaps.

TABLE I

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TABLE II

Recommendations for core asthma outcomes for NIH-initiated clinical research for adults and adolescents (≥12 years of age)

	Characterization of study population for prospective clinical trials (ie, baseline information)	**Prospective clinical trial efficacy/ effectiveness outcomes**	**Observational study outcomes***
Biomarkers	Serologic multi-allergen screen (IgE) to define atopic status (also for observational studies)	None	None
Composite Scores	Either ACQ or ACT	Either ACQ or ACT	Either ACQ or ACT
Exacerbations	Events in the 12 months prior to study entry: 1. Systemic corticosteroids for asthma 2. Asthma-specific hospital admissions 3. Asthma-specific ED visits (separate UC visits when these can be differentiated)	1. Systemic corticosteroids for asthma, for at least 3 days 2. Asthma-specific hospital admissions 3. Asthma-specific ED visits (separate UC visits when these can be differentiated) 4. Asthma-specific ICU admissions/ intubations 5. Death (all cause and asthma related)	1. Systemic corticosteroids for asthma 2. Asthma-specific hospital admissions 3. Asthma-specific ED visits (separate UC visits when these can be differentiated)
Healthcare Utilization and Costs	History of: 1. Asthma-specific hospital admissions 2. Asthma-specific ED visits 3. Asthma-specific outpatient visits 4. Asthma-specific medication use	1. Asthma-specific hospital admissions 2. Asthma-specific ED visits 3. Asthma-specific outpatient visits 4. Asthma-specific detailed medication use (name, dose, duration) 5. Resource use related to the intervention (eg, personnel time, mite eradication, equipment)	1. Asthma-specific hospital admissions 2. Asthma-specific ED visits 3. Asthma-specific outpatient visits 4. Asthma-specific detailed medication use (name, dose, duration) 5. Resource use related to the intervention (eg, personnel time, mite eradication, equipment)
Pulmonary Physiology	Spirometry (pre- and post-bronchodilator)	Spirometry (without bronchodilator)	Spirometry (pre- and post-bronchodilator)
Quality of Life	None	None	None
Symptoms	None	None	None

ACQ, Asthma Control Questionnaire; *ACT*, Asthma Control Test; *ED*, emergency department; *ICU*, intensive care unit; *NIH*, National Institutes of Health; *UC*, urgent care.

Note: For a detailed presentation and discussion of each of these outcomes, the methodology for measurement, and supporting bibliographic references, see respective article in this supplement.

* Observational study designs include cohort, case control, cross sectional, retrospective reviews, and genome-wide association studies, and secondary analysis of existing data. Some measures may not be available in studies using previously collected data.

TABLE III

Recommendations for core asthma outcomes for NIH-initiated clinical research for children (5-11 years of age)*

	Characterization of study population for prospective clinical trials (ie, baseline information)	Prospective clinical trial efficacy/ effectiveness outcomes	Observational study outcomes**
Biomarkers	Serologic multi-allergen screen (IgE) to define atopic status (also for observational studies)	None	None
Composite Scores	cACT	None	cACT
Exacerbations	Events in the 12 months prior to study entry: 1. Systemic corticosteroids for asthma 2. Asthma-specific hospital admissions 3. Asthma-specific ED visits (separate UC visits where these can be differentiated)	1. Systemic corticosteroids for asthma 2. Asthma-specific hospital admissions 3. Asthma-specific ED visits (separate UC visits when these can be differentiated) 4. Asthma-specific ICU admissions/ intubations 5. Death (all cause and asthma related)	1. Systemic corticosteroids for asthma 2.Asthma-specific hospital admissions 3. Asthma-specific ED visits (separate UC visits when these can be differentiated)
Healthcare Utilization and Costs	History of: 1. Asthma-specific hospital admissions 2. Asthma-specific ED visits 3. Asthma-specific outpatient visits 4. Asthma-specific medication use	1.Asthma-specific hospital admissions 2. Asthma-specific ED visits 3. Asthma-specific outpatient visits 4. Asthma-specific detailed medication use (name, dose, duration) 5. Resource use related to the intervention (eg, personnel time, mite eradication, equipment)	1. Asthma-specific hospital admissions 2. Asthma-specific ED visits 3. Asthma-specific outpatient visits 4. Asthma-specific detailed medication use (name, dose, duration) 5. Resource use related to the intervention (eg, personnel time, mite eradication, equipment)
Pulmonary Physiology	Spirometry (pre- and post-bronchodilator)	Spirometry (without bronchodilator)	Spirometry (pre- and post-bronchodilator)
Quality of Life	None	None	None
Symptoms	None	None	None

cACT, childhood Asthma Control Test; *ED*, emergency department; *ICU*, intensive care unit; *NIH*, National Institutes of Health; *UC*, urgent care.

Note: For a detailed presentation and discussion of each of these outcomes, the methodology for measurement, and supporting bibliographic references, see respective article in this supplement.

* Only some of these outcomes are suitable for children 0-4 years of age.

** Observational study designs include cohort, case control, cross sectional, retrospective reviews, and genome-wide association studies, and secondary analysis of existing data. Some measures may not be available in studies using previously collected data.

TABLE IV

Recommendations for supplemental asthma outcomes for NIH-initiated clinical research for adults*

	Characterization of study population for prospective clinical trials (ie, baseline information)	Prospective clinical trial efficacy/effectiveness outcomes	Observational study outcomes**
Biomarkers	1. FeNO 2. Sputum eosinophils 3. CBC (total eosinophils) 4. Total IgE 5. Allergen-specific IgE 6. Urinary LTE_4	1. FeNO 2. Sputum eosinophils 3. CBC (total eosinophils) 4. Total IgE 5. Allergen-specific IgE 6. Urinary LTE_4	1. FeNO 2. Sputum eosinophils 3. CBC (total eosinophils) 4. Total IgE 5. Allergen-specific IgE 6. Urinary LTE_4
Composite Scores	ATAQ in studies of healthcare utilization	None	ATAQ in studies of healthcare utilization
Exacerbations	1. For trials in the acute management of exacerbations (ED setting): FEV_1 2. Any prior exacerbation 3. Any prior ICU admission/ intubation 4. SES of the study population	1. For trials of acute management of exacerbations (ED setting): FEV_1	None
Healthcare Utilization and Costs	1. Categorization of asthma-specific outpatient visits: a. Primary care i. Scheduled ii. Unscheduled b. Specialty care i. Scheduled ii. Unscheduled 2. Respiratory healthcare use (pneumonia, bronchitis, etc) 3. Asthma school absences 4. Asthma work absences	1. Categorization of asthma-specific outpatient visits: a. Primary care i. Scheduled ii. Unscheduled b. Specialty care i. Scheduled ii. Unscheduled 2. Respiratory healthcare use 3. Asthma school absences 4. Asthma work presenteeism and absenteeism (WPAI instrument) 5. Cost analysis and cost-effectiveness analysis	1. Categorization of asthma-specific outpatient visits: a. Primary care i. Scheduled ii. Unscheduled b. Specialty care i. Scheduled ii. Unscheduled 2. Respiratory healthcare use 3. Asthma school absences 4. Asthma work presenteeism and absenteeism (WPAI instrument) 5. Cost analysis and cost-effectiveness analysis
Pulmonary Physiology	1. PEF monitoring 2. Airway responsiveness† 3. Lung volumes 4. Gas exchange‡	1. PEF monitoring 2. Airway responsiveness† 3. Lung volumes 4. Spirometry (pre- and post-bronchodilator) 5. Gas exchange‡	1. PEF monitoring 2. Airway responsiveness† 3. Lung volumes 4. Gas exchange‡
Quality of Life	ABP AIS-6 AQLQ-S Mini-AQLQ LWAQ Modified AQLQ-Marks SGRQ AQ-20	ABP AIS-6 AQLQ-S Mini-AQLQ LWAQ Modified AQLQ-Marks SGRQ AQ-20	ABP AIS-6 AQLQ-S Mini-AQLQ LWAQ Modified AQLQ-Marks SGRQ AQ-20
Symptoms	1. ASUI (retrospective questionnaire) 2. Daytime Symptom Diary Scale and Nocturnal Diary Scale (daily diary)	1. ASUI (retrospective questionnaire) 2. Daytime Symptom Diary Scale and Nocturnal Diary Scale (daily diary)	1. ASUI (retrospective questionnaire) 2. Daytime Symptom Diary Scale and Nocturnal Diary Scale (daily diary)

ABP, Asthma Bother Profile; *AIS-6*, Asthma Index Survey; *AQ-20*, Airways Questionnaire-20; *AQLQ-S*, Asthma Quality of Life Questionnaire-Standardized; *ASUI*, Asthma Symptom Utility Index; *ATAQ*, Asthma Therapy Assessment Questionnaire; *CBC*, complete blood count; *ED*, emergency department; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *ICU*, intensive care unit; *LTE_4*, leukotriene E_4; *LWAQ*, Living With Asthma Questionnaire; *Mini-AQLQ*, Mini Asthma Quality of Life Questionnaire; *Modified AQLQ-Marks*, Modified Asthma Quality of Life Questionnaire-Marks; *NIH*, National Institutes of Health; *PEF*, peak expiratory flow; *SES*, socioeconomic status; *SGRQ*, St George's Respiratory Questionnaire; *WPAI*, Work Productivity and Activity Impairment Questionnaire.

Note: For a detailed presentation and discussion of each of these outcomes, the methodology for measurement, and supporting bibliographic references, see respective article in this supplement.

* Only some of these outcomes are also suitable for adolescents.

** Observational study designs include cohort, case control, cross sectional, retrospective reviews, and genome-wide association studies, and secondary analysis of existing data. Some measures may not be available in studies using previously collected data.

† Methacholine inhalation and exercise challenge.

‡ Pulmonary diffusing capacity; arterial blood gases and pulse oximetry.

TABLE V

Recommendations for supplemental asthma outcomes for NIH-initiated clinical research for children*

	Characterization of study population for prospective clinical trials (ie, baseline information)	Prospective clinical trial efficacy/effectiveness outcomes	Observational study outcomes**
Biomarkers	1. FeNO 2. Sputum eosinophils 3. CBC (total eosinophils) 4. Total IgE 5. Allergen-specific IgE 6. Urinary LTE_4	1. FeNO 2. Sputum eosinophils 3. CBC (total eosinophils) 4. Total IgE 5. Allergen-specific IgE 6. Urinary LTE_4	1. FeNO 2. Sputum eosinophils 3. CBC (total eosinophils) 4. Total IgE 5. Allergen-specific IgE 6. Urinary LTE_4
Composite Scores	None	cACT	None
Exacerbations	1. For trials in the acute management of exacerbations (ED setting): a. Validated assessment tools, such as PASS, PS, PRAM, CAS, PI, ASS b. FEV_1 (ages 5-11 years, as feasible) 2. Any prior exacerbation 3. Any prior ICU admission/ intubation 4. SES of the study population	For trials in the acute management of exacerbations (ED setting): a. Validated assessment tools such as PASS, PS, PRAM, CAS, PI, ASS b. FEV_1 (ages 5-11 years, as feasible)	None
Healthcare Utilization and Costs	1. Categorization of asthma-specific outpatient visits: a. Primary care i. Scheduled ii. Unscheduled b. Specialty care i. Scheduled ii. Unscheduled 2. Respiratory healthcare use (pneumonia, bronchitis, etc) 3. Asthma school absences 4. Asthma work absences	1. Categorization of asthma-specific outpatient visits: a. Primary care i. Scheduled ii. Unscheduled b. Specialty care i. Scheduled ii. Unscheduled 2. Respiratory healthcare use 3. Asthma school absences 4. Asthma work presenteeism and absenteeism (WPAI instrument) 5. Cost analysis and cost-effectiveness analysis	1. Categorization of asthma-specific outpatient visits: a. Primary care i. Scheduled ii. Unscheduled b. Specialty care i. Scheduled ii. Unscheduled 2. Respiratory healthcare use 3. Asthma school absences 4. Asthma work presenteeism and absenteeism (WPAI instrument) 5. Cost analysis and cost-effectiveness analysis
Pulmonary Physiology	1. PEF monitoring 2. Airway responsiveness† 3. Lung volumes 4. Gas exchange‡	1. PEF monitoring 2. Airway responsiveness† 3. Lung volumes 4. Spirometry (pre- and post-bronchodilator) 5. Gas exchange‡	1. PEF monitoring 2. Airway responsiveness† 3. Lung volumes 4. Gas exchange‡
Quality of Life	1. CHSA 2. PAQLQ 3. Pediatric Caregiver AQLQ 4. PedsQL 3.0, Asthma Module	1. CHSA 2. PAQLQ 3. Pediatric Caregiver AQLQ 4. PedsQL 3.0, Asthma Module	1. CHSA 2. PAQLQ 3. Pediatric Caregiver AQLQ 4. PedsQL 3.0, Asthma Module
Symptoms	PACD (daily diary)	PACD (daily diary)	PACD (daily diary)

ASS, Asthma Severity Score; *cACT*, childhood Asthma Control Test; *CAS*, Clinical Asthma Score; *CBC*, complete blood count; *CHSA*, Child Health Survey for Asthma; *ED*, emergency department; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *ICU*, intensive care unit; *LTE_4*, leukotriene E_4; *NIH*, National Institutes of Health; *PACD*, Pediatric Asthma Caregiver Diary; *PAQLQ*, Pediatric Asthma Quality of Life Questionnaire; *PASS*, Pediatric Asthma Severity Score; *Pediatric Caregiver AQLQ*, Pediatric Caregiver Asthma Quality of Life Questionnaire; *PEF*, peak expiratory flow; *PedsQL*, Pediatric Quality of Life Inventory; *PI*, Pulmonary Index; *PRAM*, Preschool Respiratory Assessment Measure; *PS*, Pulmonary Score; *SES*, socioeconomic status; *WPAI*, Work Productivity and Activity Impairment Questionnaire.

Note: For a detailed presentation and discussion of each of these outcomes, the methodology for measurement, and supporting bibliographic references, see respective article in this supplement.

* Only some of these outcomes are also suitable for children 0-4 years of age.

** Observational study designs include cohort, case control, cross sectional, retrospective reviews, and genome-wide association studies, and secondary analysis of existing data. Some measures may not be available in studies using previously collected data.

† Methacholine inhalation and exercise challenge (children aged 5 to 7 years are less likely to perform well on these tests)

‡ Pulmonary diffusing capacity (breath holding is difficult in children aged 5 to 7 years); arterial blood gases and pulse oximetry