Asthma outcomes workshop: Overview

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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 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. (J Allergy Clin Immunol 2012;129:S1-8.)

Key words: *Asthma clinical research, National Institutes of Health asthma initiatives, standardizing outcomes*

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

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Disclosure of potential conflict of interest: W. W. Busse is on the Advisory Board for Centocor and Merck; is a consultant for Amgen, AstraZeneca, Novartis, GlaxoSmithKline, MedImmune, Genentech, and Boehringer Ingelheim; is on the Actelion Date Safety Monitoring Board; and has received research support from the National Institutes of Health (NIAID and NHLBI). W. J. Morgan is a consultant for Genentech, Novartis, and the Cystic Fibrosis Foundation; has received research support from the NIH-NHLBI CARE Network and the Cystic Fibrosis Network; and is a speaker for Phadia. The rest of the authors declare that they have no relevant conflicts of interest.

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*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)

Abbreviations used
ATS: American Thoracic Society
EC: Executive Committee
ERS: European Respiratory Society
FENO: Fractional exhaled nitric oxide
NIH: National Institutes of Health
PROMIS: Patient Report Outcomes Measurement System

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.

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 proved 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; the National Heart, Lung, and Blood Institute; the Eunice Kennedy Shriver National Institute of Child Health and Human

TABLE I. Asthma outcomes workshop participants

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(Continued)

TABLE I. *(Continued)*

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(Continued)

TABLE I. *(Continued)*

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Development; the National Institute of Environmental Health Sciences; the Agency for Healthcare Research and Quality; 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 cochairs and invited 79 asthma researchers to serve on subcommittees reflecting 7 domains of asthma outcomes, as described above. The Planning Committee also selected 2 cochairs for each subcommittee. Recognizing the various perspectives that might

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 multiallergen 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, and duration) 5. Resource use related to the intervention (eg, personnel time, mite eradication, and equipment)	1. Asthma-specific hospital admissions 2. Asthma-specific ED visits 3. Asthma-specific outpatient visits 4. Asthma-specific detailed medication use (name, dose, and duration) 5. Resource use related to the intervention (eg, personnel time, mite eradication, and equipment)
Pulmonary physiology	Spirometry (prebronchodilator and postbronchodilator)	Spirometry (without bronchodilator)	Spirometry (prebronchodilator and postbronchodilator)
Quality of life	None	None	None
Symptoms	None	None	None

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

ACQ, Asthma Control Questionnaire; *ACT*, Asthma Control Test; *ED,* emergency department; *ICU*, intensive care unit; *UC*, urgent care.

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

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. Furthermore, representatives from the fields of pharmacology, biostatistics, primary care, and behavioral/social science were included in the subcommittee membership.

The cochairs 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 cochairs, Planning Committee members, subcommittee members, discussants, and participant observers is presented in Table I. All comments by nonsubcommittee 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 on 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

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 multiallergen 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, and duration) 5. Resource use related to the intervention (eg, personnel time, mite eradication, and equipment)	1. Asthma-specific hospital admissions 2. Asthma-specific ED visits 3. Asthma-specific outpatient visits 4. Asthma-specific detailed medication use (name, dose, and duration) 5. Resource use related to the intervention (eg, personnel time, mite eradication, and equipment)
Pulmonary physiology	Spirometry (prebronchodilator and postbronchodilator)	Spirometry (without bronchodilator)	Spirometry (prebronchodilator and postbronchodilator)
Quality of life	None	None	None
Symptoms	None	None	None

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

cACT, Childhood Asthma Control Test; *ED,* emergency department; *ICU*, intensive care unit; *UC*, urgent care.

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

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

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 cochairs Drs Busse and Morgan, subcommittee members, and discussants. All other meeting participants travelled at their own expense. Contributions from National Heart, Lung, and Blood Institute; National Institute of Allergy and Infectious Diseases; Eunice Kennedy Shriver National Institute of Child Health and Human Development; National Institute of Environmental Health Sciences; and US Environmental Protection Agency provided support for publication of the workshop report.

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.

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 and 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

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 (eg, pneumonia and bronchitis) 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 (prebronchodilator and postbronchodilator) 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)

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

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; *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; *PEF*, peak expiratory flow; *SES*, socioeconomic status; *SGRQ*, St George's Respiratory Questionnaire; *WPAI*, Work Productivity and Activity Impairment Questionnaire.

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

†Observational study designs include cohort, case-control, cross-sectional, retrospective reviews; 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.

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

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 (eg, pneumonia and bronchitis) 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 (prebronchodilator and postbronchodilator) 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)

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

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; *ICU*, intensive care unit; *LTE_4*, leukotriene E_4; *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; *PS,* Pulmonary Score; *SES*, socioeconomic status; *WPAI*, Work Productivity and Activity Impairment Questionnaire.

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

†Observational study designs include cohort, case-control, cross-sectional, retrospective reviews; 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 5-7 years); arterial blood gases and pulse oximetry.

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 use these published, widely accepted standards in much the same manner as the asthma community uses 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 to 4 years, 5 to 11 years, and 12 or more years is common among asthma studies and clinical practice guidelines. However, the Exacerbations Subcommittee notes a need to distinguish adolescents (aged 12-17 years), adults 18 to 64 years old, and adults 65 years 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 and 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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Asthma outcomes: Symptoms

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Background: Respiratory symptoms are commonly used to assess the impact of patient-centered interventions.
Objective: At the request of National Institutes of Health (NIH) institutes and other federal agencies, an expert group was convened to propose which measurements of asthma symptoms should be used as a standardized measure in future clinical research studies.
Methods: Asthma symptom instruments were classified as daily diaries (prospectively recording symptoms between research visits) or retrospective questionnaires (completed at research visits). We conducted a systematic search in PubMed and a search for articles that cited key studies describing development of instruments. We classified outcome instruments as either core (required in future studies), supplemental (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: Four instruments (3 daily diaries, 1 for adults and 2 for children; and 1 retrospective questionnaire for adults) were identified. Minimal clinically important differences have not been established for these instruments, and validation studies were only conducted in a limited number of patient populations. Validity of existing instruments may not be generalizable across racial-ethnic or other subgroups.
Conclusions: An evaluation of symptoms should be a core asthma outcome measure in clinical research. However, available instruments have limitations that preclude selection of a core instrument. The working group participants propose validation studies in diverse populations, comparisons of diaries versus retrospective questionnaires, and evaluations of symptom assessment alone versus composite scores of asthma control.
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Key words: *Asthma Symptom Utility Index, Asthma Symptom Diary Scales, Pediatric Asthma Caregiver Diary*

Abbreviations used
ADSS: Asthma Disease Severity Scale
ASUI: Asthma Symptom Utility Index
ATS: American Thoracic Society
ED: Emergency department
ERS: European Respiratory Society
ICC: Intraclass correlation coefficient
NIH: National Institutes of Health
PACD: Pediatric Asthma Caregiver Diary
PASDS: Pediatric Asthma Symptom Diary Scale
PSRS: Physician Severity Rating Scale
QOL: Quality of life
SABA: Short-acting β-agonist
SES: Socioeconomic status
SFD: Symptom-free day

Asthma clinical research lacks adequate outcomes standardization. As a result, our ability to examine and compare outcomes across clinical trials and clinical studies, interpret evaluations of new and available therapeutic modalities for this disease at a scale larger than a single trial, and pool data for observational studies (eg, genetics, genomics, and pharmacoeconomics) is impaired.[5] Several National Institutes of Health (NIH) institutes that support asthma research (the National Heart, Lung, and Blood Institute; National Institute of Allergy and Infectious Diseases; National Institute of Environmental Health Sciences; and Eunice Kennedy Shriver National Institute of Child Health and Human Development), as well as the Agency for Healthcare Research and Quality, have agreed to an effort for outcomes standardization. This effort aims at (1) establishing standard definitions and data collection methodologies for validated outcome measures in asthma clinical research with the goal of enabling comparisons across asthma

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Disclosure of potential conflict of interest: R. F. Lemanske, Jr, is a speaker for Merck and AstraZeneca and has consulted for AstraZeneca, Map Pharmaceuticals, Gray Consulting, Smith Research Inc, Merck Childhood Asthma Network, Novartis, Quintiles/Innovax, RC Horowitz & Co Inc. Scienomics, Scientific Therapeutics, Cognimed Inc, SA Boney and Associates, GlaxoSmithKline, and Double Helix Development Inc. K. S. Elward is a speaker on guidelines implementation for Merck; has received research support from the National Asthma Control Initiative; is a member of the Virginia Asthma Coalition; and is a member of the National Asthma Education and Prevention Program Coordination Committee. M. Kattan has received research support from the NIH-NIAID. The rest of the authors declare that they have no relevant conflicts of interest.

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TABLE I. Recommendations for classifying symptoms measures/instruments for NIH-initiated clinical research

	Characterization of study population for prospective clinical trials (ie, baseline information)	Prospective clinical trial efficacy/effectiveness outcomes	Observational study outcomes*
Adults			
Core outcomes	None	None	None
Supplemental outcomes	1. ASUI (retrospective questionnaire)[1] 2. Daytime Symptom Diary Scale and Nocturnal Diary Scale (daily diary)[2]	1. ASUI (retrospective questionnaire)[1] 2. Daytime Symptom Diary Scale and Nocturnal Diary Scale (daily diary)[2]	1. ASUI (retrospective questionnaire)[1] 2. Daytime Symptom Diary Scale and Nocturnal Diary Scale (daily diary)[2]
Emerging outcomes	1. Various symptom derivatives: SFDs, episode-free days, maximum symptom days, asthma control days	1. Various symptom derivatives: SFDs, episode-free days, maximum symptom days, asthma control days	1. Various symptom derivatives: SFDs, episode-free days, maximum symptom days, asthma control days
Children			
Core outcomes	None	None	None
Supplemental outcomes	PACD (daily diary)[3]	PACD (daily diary)[3]	PACD (daily diary)[3]
Emerging outcomes	1. Electronic PASDS (daily diary)[4] 2. Various symptom derivatives: SFDs, episode-free days, maximum symptom days, asthma control days	1. Electronic PASDS (daily diary)[4] 2. Various symptom derivatives: SFDs, episode-free days, maximum symptom days, asthma control days	1. Electronic PASDS (daily diary)[4] 2. Various symptom derivatives: SFDs, episode-free days, maximum symptom days, asthma control days

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

research studies and clinical trials and (2) identifying promising outcome measures for asthma clinical research that require further development. In the context of this effort, 7 expert subcommittees were established to propose and define outcomes under 3 categories—core, supplemental, and emerging:

- *Core outcomes* are identified as a selective set of asthma outcomes to be considered by participating NIH institutes and other federal agencies as requirements for institute/agency-initiated funding of clinical trials and large observational studies in asthma.
- *Supplemental outcomes* are asthma outcomes for which standard definitions can or have been developed, methods for measurement can be specified, and validity has been proved but whose inclusion in funded clinical asthma research will be optional.
- *Emerging outcomes* are asthma outcomes that have the potential to (1) expand and/or improve current aspects of disease monitoring and (2) improve translation of basic and animal model–based asthma research into clinical research. Emerging outcomes may be new or may have been previously used in asthma clinical research, but they are not yet standardized and require further development and validation.

Each subcommittee used the recently published American Thoracic Society (ATS)/European Respiratory Society (ERS) Statement: Asthma Control and Exacerbations—Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice[6] (hereafter referred to as the ATS/ERS statement) as a starting point and updated, expanded, or modified its recommendations as the subcommittee deemed appropriate. Each subcommittee produced a report that was discussed, modified, and adopted by the Asthma Outcomes Workshop that took place in Bethesda, Md, on March 15 and 16, 2010. The reports were revised accordingly and finalized in September 2011. The workshop's recommendations in regard to asthma symptoms are presented in this article.

Respiratory symptoms of asthma (eg, dyspnea, cough, wheeze, and chest tightness) are used to diagnose the disease and to

TABLE II. Methods for measuring and reporting asthma symptoms

Instrument	Measure/report method
PACD, supplemental measure For: caregivers of 2- to 5-year-old children	Measure: daily diary completed by caregivers ● Daytime symptoms, activity limitation, need for UC, and SABA use (7 items; 0-5 point scale) ● Nighttime symptoms, impact on caregiver, and SABA use (3 items; 0-5 point scale) Report as: ● Mean daytime and nighttime symptoms ● MCID not established
Daytime Symptom Diary Scale and Nocturnal Diary Scale, supplemental measure For: adults	Measure: daily diary completed by patient ● Daytime symptoms (4 items; 0-6 point scale) ● Nocturnal awakening (1 item; 0-3 point scale) Report as: ● Mean scores (daily, weekly) ● Change over time is the difference between mean score from a 2-week baseline and a 2-week subsequent period ● MCID not established
ASUI, supplemental measure For: adults	Measure: retrospective questionnaire of previous 2 weeks ● 11 items on frequency and severity of asthma symptoms (8 items) and side effects (3 items) Report as: ● Scoring uses a table (see instrument's development publication) for converting patient reported data into utilities (range, 0-1) ● Mean scores ● Change in mean scores ● MCID not established

MCID, Minimal clinically important difference; *UC,* urgent care.

TABLE III. Key points and recommendations

1. An evaluation of symptoms should be a core outcome measure for asthma clinical research; however, available instruments have significant limitations that preclude selection of a core instrument. Supplemental instruments are recommended for standardized symptom measures; their use would depend on the research question and study circumstances.
2. To select a core instrument, the following information is needed: (1) validation in diverse populations, especially racial and ethnic minority populations; (2) evidence for the comparative utility of diaries and retrospective questionnaires; and (3) evidence for the superiority (in sensitivity and reliability, as well as impact on study burden) of assessment of symptoms alone compared with assessment as a part of a composite score of asthma control.
3. Asthma symptoms can be measured via *daily diaries* (in which study participants and/or caregivers are asked to prospectively record symptoms between research visits) or *retrospective questionnaires* (in which study participants and/or caregivers complete questionnaires at research visits).
4. Many asthma studies report on asthma symptom measures, lung function, and biomarkers as separate outcomes, but studies generally do not compare the outcome measures to each other, such as correlations between symptom scores and lung function. The only asthma studies that compare symptom measures directly to lung function are the studies that were designed to evaluate the validity of asthma symptom instruments. Thus it is not currently possible to conclude whether additional clinically important information is obtained by the use of symptoms measures.
5. There is insufficient information to directly compare the value of daily symptom diaries to retrospective symptom questionnaires for asthma clinical trials.
6. Only a small number of asthma symptom instruments have undergone an evaluation to assess validity. In many asthma studies, including clinical trials, instruments used to assess symptoms are poorly described and/or have undefined psychometric properties. Therefore it was necessary to rely primarily on the content knowledge of the subcommittee members for identifying such instruments for this report. The subcommittee recommends that published studies include the names and sources of the symptom instruments used and information about whether the instrument has been validated. Such information will facilitate cross-study synthesis of research data and an independent assessment of the validity of study findings regarding asthma symptoms.
7. Asthma studies generally report symptoms using the symptom scales as originally designed for the instrument (ie, a scale of symptom frequency or intensity). However, studies have also reported various derivatives (eg, "symptom-free day" and "maximum symptom day") based on alternate approaches to data analyses. Because there is no consensus about the measurement and/or reporting of such derivatives, the subcommittee considers these endpoints as emerging outcomes.
8. There is substantial evidence that daily diaries, particularly if used as paper and pencil versions, may be unreliable. Electronic diaries offer an opportunity to overcome some limitations of paper and pencil daily diaries, but the former are currently too costly and cumbersome for routine use.

monitor response to treatment and disease control. Symptoms can be measured alone or as part of a composite measure that includes other asthma outcomes, such as activity limitation or lung function. Daily diaries (in which study participants and/or caregivers are asked to prospectively record symptoms between research visits) and retrospective questionnaires (in which study participants and/or caregivers complete questionnaires at research visits) about asthma symptoms are commonly used in clinical research to assess patient-centered outcomes.

The task for the Asthma Symptoms Subcommittee was to identify and review the validity of tools that attempt to assess asthma symptoms alone. Subcommittee members conducted a comprehensive review of the literature to identify validated daily diaries and retrospective questionnaires about symptoms in children and adults with asthma (see the subsequent section "Validity and reliability of instruments").

Three daily diaries (all developed by the same group) and 1 retrospective questionnaire were identified. The subcommittee considered the importance of assessing respiratory symptoms as an asthma outcome, the validity of instruments developed to assess asthma symptoms, and the potential to standardize the measurement of asthma symptoms in clinical research. The results and recommendations are summarized in Tables I[1-4], II, and III.

REVIEW OF SYMPTOMS AS AN OUTCOME MEASURE

Definitions

Asthma symptoms are measured by patient or caregiver report, via self-administered paper or electronic diaries or questionnaires, or interviewer-administered questionnaires. A variety of considerations influence the measurement of asthma symptoms in research studies. For example, should each commonly recognized symptom of asthma (eg, cough, wheeze, shortness of breath, and chest tightness) be assessed individually, or should a composite overall score of daily symptom burden be recorded? What numeric scale of symptom severity should be used (eg, 1-3 or 0-10)? How reliable are the scores obtained from symptom diaries since it has been documented that some participants complete their diaries right before their study visit rather than on a daily basis? For interviewer-administered retrospective questionnaires, have recall and/or recall bias been related to the timeframe over which the participant is asked to report symptoms?

We conducted a review of the literature with the following objectives:

- to identify and evaluate the validity of daily symptom diaries used in asthma clinical research,
- to identify and evaluate the validity of retrospective symptom questionnaires used in asthma clinical research, and
- to determine whether daily symptom diaries add value in documenting the adequacy of asthma treatment (ie, control of symptoms) compared with retrospective symptom questionnaires.

Search methodology

The literature search was conducted in 2 stages.

Stage 1: Key word-driven search. We conducted 2 key word searches using different search terms. The first search was aimed at identifying articles related to symptom diaries and the second at identifying articles related to symptom questionnaires. This approach yielded a total of 383 articles for the search on diaries and 444 articles for the search on questionnaires. Overlap was extensive, with 259 articles appearing in both searches. The final search strategy used was as follows:

TABLE IV. Key articles on validated instruments for measuring asthma symptoms

Key article with validated instrument	No. of citations	No. of full-text reviews
Symptom diary		
Santanello NC, Barber BL, Reiss TF, Friedman BS, Juniper EF, Zhang J. Measurement characteristics of two asthma symptom diary scales for use in clinical trials. Eur Respir J. 1997;10(3):646-51.	79	45
Santanello NC, Davies G, Galant SP, Pedinoff A, Sveum R, Seltzer J, et al. Validation of an asthma symptom diary for interventional studies. Arch Dis Child. 1999;80(5):414-20.	58	18
Santanello NC, Demuro-Mercon C, Davies G, Ostrom N, Noonan M, Rooklin A, et al. Validation of a pediatric asthma caregiver diary. J Allergy Clin Immunol. 2000;106(5):861-6.	20	10
Symptom questionnaire		
Revicki DA, Leidy NK, Brennan-Diemer F, Sorensen S, Togias A. Integrating patient preferences into health outcomes assessment: the multiattribute Asthma Symptom Utility Index. Chest. 1998;114(4):998-1007.	80	21
Total	237	94

(*asthma control questionnaire* OR *asthma control test* OR *asthma symptom questionnaire** OR *asthma questionnaire** OR *asthma daytime symptom questionnaire** OR *asthma nocturnal symptom questionnaire**)

OR

(*asthma* OR *asthmatic**) AND (*symptom questionnaire** OR *daytime symptom questionnaire** OR *daytime questionnaire scale** OR *nocturnal symptom questionnaire** OR *nocturnal questionnaire scale**)

OR

(*asthma* OR *asthmatic*) AND (*symptom component index** OR *symptom component indices*)

OR

(*asthma* OR *asthmatic*) AND (*control day** OR *maximum symptom day** OR *episode of poor asthma control**).

The titles and abstracts of the articles were reviewed in an attempt to identify instruments related to asthma symptoms. Few instruments were identified from these searches, however, because titles and abstracts rarely describe whether information on asthma symptoms was collected or how the information was used. We concluded that a key word–driven search was not an effective or efficient method of identifying articles of interest. Therefore we adopted a citation search as an alternate approach to searching for relevant literature.

Stage 2: Citation search. Subcommittee members identified key articles that describe the development or use of daily symptom diaries or retrospective symptom questionnaires. Only instruments that had been validated were considered suitable for this search. We then conducted a forward search of all articles that cited each key article under the assumption that authors would cite the original work on developing an instrument when using it. This approach allowed us to provide complete information about both the development and use of validated daily asthma symptom diaries and retrospective symptom questionnaires.

The searches conducted in Stages 1 and 2 were limited to English-only original empiric research articles in the Cumulative Index to Nursing and Allied Health Literature, the Cochrane Collaboration, MEDLINE, PsycINFO, and Web of Science that were published in the years 1990 to 2009. Articles that mentioned a measure but did not use it to inform study results were not examined. This report expands the ATS/ERS statement, as it extends the review to the year 2009 and includes reports in children younger than age 6 years, whereas the ATS/ERS statement reviewed studies published from 1998 to 2004 and reviewed studies of children aged 6 years and older.

Search results

Four key articles were identified for the forward citation search and review (see Table IV).[1-4] We then reviewed abstracts for articles in the forward search to isolate a subset that used the symptom instrument as an outcome measure and reviewed the full text of the articles in this subset. The number of full-text reviews for each key article is also shown in Table IV.

This citation review yielded 4 asthma symptom instruments that included validation studies (3 daily symptom diaries and 1 retrospective symptom questionnaire; see Table V).

For each of these instruments, information was summarized into an abstract with the following fields:

- symptoms used as primary or secondary endpoint in study;
- objective of study;
- study design;
- description of symptom instrument (including source, if cited);
- study sample description (including age, sex, race/ethnicity, income);
- asthma severity (including severity score if available);
- sample size;
- state (if United States) or country;
- description of symptom outcome measure based on key article; and
- study results related to symptoms, lung function, biomarkers, exacerbations, acute care utilization (eg, emergency department [ED] visits), medication use.

Validity and reliability of instruments

To evaluate the validity and reliability of each instrument, we examined various psychometric properties. In this article we focus our discussion of the instruments on the following aspects.

Validity. Validity is defined as the ability of an outcome to measure the underlying concept that it aims to measure.[7] Although there are several aspects of validity, the articles we reviewed focused on *construct validity* as the relation of an instrument to other instruments or measures with which it is expected to be associated and *convergent validity* as the correlation of the instrument with other measures of the same or similar nature.

Internal consistency. Internal consistency is a measure of reliability that refers to the consistency among the different

TABLE V. Validated instruments for measuring symptoms of asthma

Author, year	Santanello et al, 2000	Santanello et al, 1999	Santanello et al, 1997	Revicki et al, 1998
Type of instrument	Daily diary	Daily diary	Daily diary	Retrospective questionnaire
Name of instrument	PACD	PASDS	Daytime Symptom Diary Scale; Nocturnal Diary Scale	ASUI
For children or adults	Children aged 2-5 years	Children aged 6-14 years	Adults	Adults
Completed by self or by caregiver	Caregiver	Child; some assistance from parents allowed; second-grade reading level	Self	Self
Requires permission for use (eg, copyright)	Yes, Merck & Co	Yes, Merck & Co	Yes, Merck & Co	No
Cost (unit price)	Not stated	Not stated	Not stated	None
Electronic or paper	Paper	Electronic	Paper	Paper

items constituting a measure; in other words it is the extent to which all the items measure the same concept. This value is captured by correlating responses to different items within the measure. Internal consistency was most frequently reported as a Cronbach α statistic, which ranges from 0 to 1. A Cronbach α coefficient value between 0.75 and 0.95 indicates good internal consistency.[2]

Test-retest reliability. Test-retest reliability refers to the stability of a measurement over short periods of time during which the underlying construct is assumed to be stable. If the scores are expected to be stable, the test-retest reliability should be high. Test-retest reliability for continuous variables is usually expressed as a correlation between measurements in the same individual at different time points. An intraclass correlation coefficient (ICC) is used for this purpose. A value above 0.70 is considered acceptable for an instrument used in research. For dichotomous variables, test-retest reliability is measured with the κ statistic.

Responsiveness or sensitivity to change. Responsiveness or sensitivity to change of an outcome is defined as how the outcome varies when clinically meaningful changes occur.[7] In asthma research related to symptoms, responsiveness is most frequently evaluated by examining change in measure scores in response to treatment. If a study provides evidence that a symptom score changes with appropriate treatment (a treatment that is expected to have a clinically meaningful effect), this finding could be considered evidence of the measure's responsiveness.

Medical and scientific value

The subcommittee considers symptoms to be a significant manifestation of asthma and an important patient-oriented outcome. However, the subcommittee's review of instruments to measure symptoms raised significant questions regarding their classification as core, supplemental, or emerging outcome measures. Despite the frequent use of symptom diaries or questionnaires, it is not clear how much additional information they contribute either independently or collectively to other outcome measures, such as pulmonary function, biomarkers, respiratory exacerbations, or combinations of outcome measures (eg, composite scores of asthma control, which include symptoms as well as other manifestations of asthma, such as the Asthma Control Test [see the Composite Scores of Asthma Control article]) that are commonly assessed in clinical research. In addition, many trials employ "homemade" instruments to assess symptoms (ie, newly derived endpoints, such as asthma-free days, based on alternative analysis of the data collected by the instruments) that have neither been formally validated as an outcome measure nor described in published manuscripts, raising questions about the value of such assessments and precluding comparisons across studies. There is also limited validation of instruments in diverse populations, which is problematic given differences in symptom perception and reporting across different patient subgroups.[8-10] Furthermore, evidence of minimal clinically important difference in a change in symptoms in longitudinal studies is largely lacking. Finally, the routine use of either symptom diaries or questionnaires introduces a level of participant and study personnel (eg, study coordinator) burden that needs to be evaluated in the context of the value of that information relative to other indices in asthma health. In short, the researcher must consider whether this burden is really worth the effort.

Future directions and key research questions

1. Titles, abstracts, and key words of published studies rarely indicate whether a study collected information on asthma symptoms, how this information was collected (ie, the name of the instrument) or how the information was used. The methods sections of these studies also frequently fail to describe this information or do so only inadequately. As a result, the key word–based literature search identified few instruments that assess symptoms. The name of the instrument(s) used to measure symptoms should be reported in the methods section; information about the validity of such instruments also should be reported, where available. If the abstract includes information about asthma symptoms, the instrument used to measure symptoms should be identified in the abstract as well.
2. Studies are needed that compare the added value of measuring symptoms alone with measuring them as part of other outcomes (ie, asthma composite scores such as the Asthma Control Test or Asthma Control Questionnaire [see the Composite Scores of Asthma Control article]).
3. Completing daily diaries imposes a substantial burden on study participants and research staff (eg, ensuring that

diaries are completed and data are entered). Studies are needed to directly compare the value of daily diaries with that of retrospective questionnaires in asthma clinical research.
4. Instruments to measure asthma symptoms have not been tested adequately in diverse patient populations (eg, populations that differ by race/ethnicity, socioeconomic status [SES], or health literacy). Given the burden of asthma in particular subpopulations (eg, racial/minorities and those with low SES and low health literacy), existing instruments need to be validated in these groups.

REVIEW OF SPECIFIC ASTHMA SYMPTOM QUESTIONNAIRES

This section summarizes each of the 4 asthma symptom questionnaires (3 daily diaries, 1 retrospective questionnaire) that were supported by validation studies. For each questionnaire, we present the methods used to develop the questionnaire; the range of scores; the internal consistency and test-retest reliability; validity; responsiveness; and practicality and risk.

Electronic Pediatric Asthma Symptom Diary Scale (developed by N. C. Santanello et al[4])

Summary

1. Although parent/caregiver-completed reports of children's asthma symptoms are valuable, self-reported information has inherent value in accurately assessing the child's experience and response to treatment. The electronic Pediatric Asthma Symptom Diary Scale (PASDS) is therefore of significant interest.
2. The electronic PASDS is the only symptom instrument specifically validated with the use of an electronic diary, which may improve data quality.
3. The scoring scale seems inadequate in that the mean scores were all well below 1.0 on a scale of 0 to 5 for the daytime symptom scale. Thus there may be a floor effect that limits the value of this instrument.
4. Limited information regarding the study population used to develop and validate the instrument suggests the results may not be broadly applicable in children aged 6 to 14 years (the age range of the population studied).
5. More information about the psychometric properties is needed.
6. Recommendation for use in NIH-initiated asthma studies: The subcommittee recommends classifying the electronic PASDS as an emerging instrument for the symptom outcome measure.

Methods. The authors intended to develop a validated asthma symptom daily diary scale for use as an outcome measure of asthma treatment in a clinical trial of children aged 6 to 14 years. The study population was primarily white, and 70% were male; information about SES was not reported.

The authors used items from a previously validated adult symptom diary scale, nonvalidated pediatric diaries in the literature, and the diary card from the Childhood Asthma Management Program trial.[11] Interviews with children were used to select appropriate wording. The overall score is based on a daytime symptom scale consisting of 3 questions (trouble breathing, asthma bother, and activity limitation) and a question regarding awakening with asthma.

Range of values and scoring. The 3 daytime symptom questions could be scored as 0 to 5 (where 0 = no bothersome symptoms and 5 = symptoms very bothersome all the time). The single nocturnal symptom item could be scored as 0 to 3 (where 0 = no awakenings and 3 = awake all night).

Internal consistency and test-retest reliability. Information regarding internal consistency was not provided. Test-retest reliability was assessed with the ICC using data for all 106 patients from study week 2 (visit 3) and study week 3 (visit 4) diary data. This period was hypothesized to be a period of time when the patients' asthma would be stable. The ICC values were acceptable for the frequency and bother of daytime asthma symptoms questions. The ICCs for the daytime questions were 0.76 (95% CI, 0.67-0.83) for the trouble breathing question, 0.77 (95% CI, 0.68-0.84) for the asthma bother question, and 0.72 (95% CI, 0.61-0.80) for the activity limitation question. The combined asthma symptom scale had an ICC value of 0.77 (95% CI, 0.68-0.84). The nighttime awakening question did not perform as well on test-retest reliability as the 3 daytime symptom questions or the combined scale (ICC, 0.56; 95% CI, 0.41-0.68).

Validity. The instrument scores were not significantly correlated with the measure of FEV_1. The authors make the case that FEV_1 has not been found to correlate with changes in asthma symptoms, but the references they cite actually provide little support for their assertions. For example, their citation of McFadden[12] pertains only to acute (emergent) exacerbations and not to the population they studied. The mean FEV_1 was 82.5% in the "stable" group. Thus airflow obstruction was considerably more severe in a subgroup of study participants than in other studies of children (eg, studies of mild persistent asthma in which the FEV_1 is over 93% predicted value [Childhood Asthma Management Program and Personalized Assessment and Control Tool]).[11,13] The lower FEV_1 in this subgroup of participants may help explain why symptom scores were not associated with FEV_1: there is evidence that blunted perception of airflow obstruction occurs in patients with more severe disease.[8,14] All 3 daytime symptom questionnaires discriminated between stable and new-onset/worse groups at baseline, but the short duration of the trial was insufficient for evaluation of longitudinal validity.

Over the short-term, the changes in symptom diary scores showed strong associations with the interventions given to participants in the new onset/worse group, suggesting that the diary could reflect response to treatment (in this case, improvements) in patient symptoms.

Responsiveness. The combined daytime symptoms score was sensitive to changes in treatment, as was the single question related to "bother of asthma symptoms." Subsequent work by this author and her team[4] suggested that a measurement of −0.31 would be a statistically important change for this measure.

Practicality and risk. The diary seems very easy to use in the target population. The questions are simple and should be easy to use with children 6 to 14 years old (Fleisch Reading Ease scale of second-grade level). Use of an electronic diary is a considerable strength of this instrument; it may help improve accuracy and completeness of the symptom diary, but this improvement would need to be demonstrated in a more broadly selected population. Use of this instrument has minimal risk.

Pediatric Asthma Caregiver Diary (developed by N. C. Santanello[3])

Summary

1. The Pediatric Asthma Caregiver Diary (PACD) was developed for use by caregivers of children aged 2 to 5 years with persistent asthma, and it has relatively good measurement characteristics in this population.
2. It is not known whether results are generalizable across asthma severity categories or demographic groups that vary from the study population, which was largely white.
3. Although the maximum score was 5 for the diary, participants generally reported scores of 0 or 1. Mean scores that combined symptom and activity scores were almost always less than 1. Although results seem to be sensitive to treatment, there may be a floor effect that limits the value of this instrument.
4. As with all caregiver/parent-reported symptoms, caregivers or parents may underreport symptoms because of a desire to appear to have taken good care of their child's asthma.
5. Recommendation for use in NIH-initiated clinical trials: The subcommittee recommends classifying the PACD as a supplemental instrument for symptom outcome measure.

Methods. The authors developed and tested the PACD as an asthma symptom diary for young children (aged 2-5 years); the PACD was the only published diary found in our literature review that was developed for use in this pediatric population. The PACD was based on a previously developed asthma symptom diary for children aged 6 to 14 years[2] and included 3 daytime symptom questions (cough, wheeze, and trouble breathing), an activity limitation question, and questions to capture nocturnal symptoms. In the validation study,[3] at baseline, children were classified as either stable (no requirement for change in anti-inflammatory therapy) or unstable (anti-inflammatory therapy added or increased).

Range of values and scoring. The PACD scores can be calculated and reported in several ways: (1) individual scores for each item, (2) an overall mean score, and (3) derivatives, such as symptom-free days (SFDs). Each daytime symptom question and the activity limitation question are scored on a 6-point scale, from 0 to 5. For an overall mean score, the mean of the 3 daytime symptom questions and the activity limitation question are calculated. Scores for each question and for the symptom/activity measure range from 0 to 5 in populations of children with stable and unstable asthma. In the validation study[3] for the instrument, mean scores for individual symptom items were less than 1 among the study group considered to have unstable asthma, except for the "severity of cough" item, for which the mean score was 1.37; this finding suggests the possibility of a floor effect (ie, the inability to detect further improvements in symptoms).

Days without asthma symptoms, or SFDs, are defined as a day without asthma symptoms, short-acting β-agonist (SABA) use, systemic corticosteroid use, or need for urgent asthma care. Among the study group with stable asthma, the mean percentage of SFDs was 37%, and among those with unstable asthma, it was 11%.

Validity. The validation study focused on the daytime symptom questions and the activity limitation question. The instrument was used over a 3-week period in children with persistent asthma; 1 group was identified to have unstable asthma at the beginning of the study, and the other group's asthma was considered stable. The design created a potential for bias because investigators classifying children as stable or unstable were not independent from the investigators who developed the questionnaire. The PACD values were compared between groups and within groups over time, as well as to external measures, such as caregiver quality of life (QOL), SABA use, and physician asthma severity rating.

In the absence of a gold standard, the authors correlated PACD values and results from the pediatric asthma caregiver QOL questionnaire,[15] as well as physician global assessment of change in asthma. Correlations were small but statistically significant between the PACD asthma symptom score and the activity and emotion domains of the QOL questionnaire (−0.27 and −0.34, respectively). Daytime cough had a correlation of −0.23 with the activity domain of the QOL questionnaire and was statistically significant. The correlation between daytime wheeze and trouble breathing was not significant. The PACD correlates with some other measures of asthma status, in particular days of SABA use and physician global assessment of change in asthma.

The change in PACD scores over the 3-week period was strongly correlated with the change in SABA use (0.46-0.67). The PACD was weakly associated with other measures of asthma status, including pediatric caregiver QOL scores and physician global assessment of change in asthma over the 3-week observation period.

Since the 2000 publication of the validation study, the PACD has been used as an outcome measure in 10 published studies. Although 1 multinational study used the PACD,[16] the majority of studies using the PACD have enrolled a largely white pediatric population. Validation of the PACD in other populations would be desirable before it could be recommended as a valid instrument for routine use in measuring symptoms. Information about the PACD was not included in the ATS/ERS statement, as the ATS/ERS statement focused on adults and children aged 6 years and older.[6]

Internal consistency and test-retest reliability. The daytime symptoms and activity limitation questions had good internal consistency, with a Cronbach α coefficient of 0.90. Among children with stable asthma, test-retest reliability was fair for individual items (ICC, 0.53-0.81) but was acceptable for the symptom/activity limitation composite score (ICC, ≥0.75). Among children with unstable asthma, test-retest reliability was not acceptable (ICC, 0.44-0.69), but this finding may be due to the increased variability in asthma symptoms over time in this group compared with the stable group.

The PACD appears to have similar scores across populations with similar disease activity. The instrument was used in a multinational randomized clinical trial of more than 600 preschool children with asthma, and mean baseline scores for the daytime symptom and activity limitation questions were similar to those in the original validation population for the PACD. Two other studies of preschool children with intermittent asthma showed similarly low PACD scores during periods of stable asthma.[17,18]

Responsiveness. The PACD individual questions and symptom/activity limitation scores improved after therapeutic intervention in preschool children with unstable asthma. This improvement was accompanied by a reduction in SABA use. The unstable asthma group had a mean reduction in SABA treatments of 0.53 compared with a mean increase in SABA treatments of 0.12 in the stable asthma group. The PACD question scores also demonstrated responsiveness to treatment in a larger multicenter clinical trial of 238 preschool children in the United States.[18]

TABLE VI. Longitudinal construct validity[2]

	Pearson correlation coefficients (95% CI)					
	Clinical trial A (n = 239)			Clinical trial B (n = 104)		
Diary type	FEV_1	PEFR	SABA inhaler puffs	FEV_1	PEFR	SABA inhaler puffs
Daytime scale	−0.28 (−0.39 to −0.16)	−0.49 (−0.58 to −0.38)	0.64 (0.56 to 0.71)	−0.25 (−0.42 to −0.06)	−0.38 (−0.53 to −0.20)	0.58 (−0.43 to 0.69)
Nocturnal scale	−0.38 (−0.48 to −0.26)	−0.32 (−0.43 to −0.20)	0.48 (0.37 to 0.57)	−0.28 (−0.45 to −0.09)	−0.51 (−0.64 to −0.35)	0.47 (0.30 to 0.61)

Practicality and risk. The instrument is easy to use. Measurement has minimal risk.

Daytime Symptom Diary Scale and Nocturnal Diary Scale (developed by N.C. Santanello et al[2])

Summary

1. The Daytime Symptom Diary Scale and Nocturnal Diary Scale have relatively good measurement characteristics for use in adults with asthma.
2. Results seem to be sensitive to treatment.
3. It is not known whether results are generalizable across asthma severity categories or demographic groups that vary from the study population.
4. Recommendation for use in NIH-initiated clinical trials: The subcommittee recommends these scales as a supplemental outcome.

Methods. The Daytime Symptom Diary Scale and the Nocturnal Diary Scale were developed by consensus from items used in previous trials and then assessed in 2 clinical trials of a noninhaled corticosteroid investigational asthma drug. Study participants were aged 18 to 65 years, with mild to moderate asthma. All had a history of asthma, a measure of FEV_1 40% to 80% of predicted levels, and evidence of reversibility of airway obstruction after inhaled SABA. Patients were allowed use of SABA inhalers on an as-needed basis.

The Daytime Symptom Diary Scale assesses (1) frequency of general asthma symptoms, (2) inconvenience of asthma symptoms, (3) frequency of limitation during usual activities, and (4) frequency with which asthma symptoms limit the ability to perform usual activities. Patients also record number of actuations of SABA and measure and record the best of 3 peak expiratory flow rates (PEFRs).

The Nocturnal Diary Scale assesses awakenings with asthma symptoms completed on arising in the morning. Participants record the number of actuations of SABA from a metered-dose inhaler that was used after going to sleep for the night and record the best of 3 PEFRs on arising in the morning.

Range of values and scoring. The Daytime Symptom Diary Scale ranges from 0 (none of the time) to 6 (all of the time). The Nocturnal Diary Scale ranges from 0 (no awakening with asthma symptoms) to 3 (awake all night). Daytime scores are computed as the average of the 4 questions on the daytime symptom scale and the weekly score as the average of the daily daytime scale scores. Nocturnal scores are computed in a similar manner. A decrease in the weekly score for the daytime and nocturnal scales indicates an improvement in asthma symptoms. The change from baseline in the asthma scale scores is computed as the difference between the average score from the last 2 weeks of the placebo run-in period and the last 2 weeks of the active treatment phase in the 2 clinical trials.

Internal consistency and test-retest reliability. The daytime scale showed a high level of internal consistency in both studies (Cronbach $\alpha = 0.92$ and 0.90) and borderline acceptable reliability (ICC, 0.69 and 0.74). Internal consistency for the nocturnal scale is not applicable because this scale consists of only 1 question. The Nocturnal Diary Scale showed stronger reliability than the daytime scale in both studies (ICC, 0.83 and 0.87).

Validity. Instrument values were moderately to strongly correlated in the expected direction with change in symptoms on the asthma symptom scales and change in FEV_1, PEFR, and puffs of SABA inhaler use (Table VI). As the average change in symptom scale score decreased (improved), the average change in FEV_1 and PEFR increased (improved), and puffs of inhaler decreased (improved). Correlations were strongest between the symptom scale scores and puffs of SABA inhaler used and weakest between the symptom scale scores and FEV_1, which was measured weekly at clinic visits.

The instruments were developed in predominantly male adult asthma populations (59% and 67% of participants); few additional demographic data are reported.

Responsiveness. The responsiveness of the daytime and nocturnal diary scales varied with drug treatment. The daytime and nocturnal scales were responsive to change across the drug dose groups in 1 study (P for trend < .05) but not significantly different between study treatment and placebo in the other study ($P > .10$). Consistent with the responsiveness of the symptom scales, the average change in the asthma measures of FEV_1, PEFR, and SABA inhaler use showed greater improvements in the drug-treated groups than in the placebo-treated group.

Practicality and risk. The instruments are brief and of apparently low burden on participant, study personnel (eg, study coordinator), and analyst resources. Use of this instrument is minimal in risk.

Asthma Symptom Utility Index (developed by D. A. Revicki et al[1])

Summary

1. The Asthma Symptom Utility Index (ASUI) is a retrospective symptom questionnaire for adults. It consists of 11 items designed to assess the frequency and severity of 4 asthma symptoms (cough, wheeze, dyspnea, and nocturnal awakening), as well as side effects, weighted according to patient preferences.

2. The ASUI is 1 of the most tested symptom measures reported in the literature, including use in French, English, and Italian adults. The ASUI has good measurement characteristics for use in adults with asthma.
3. Results indicate that the ASUI is sensitive to change over different levels of severity.
4. The ASUI scoring requires a complex calculation of a product of 5 values, weighted by patient preferences.
5. The scale is constructed based on weights assigned to different preferences; these weights might not be generalizable to other groups diverse in ethnicity, culture, or SES.
6. There is a need for studies, particularly for this measure, that can determine empirically which scores are associated with clinically significant improvement.
7. Recommendation for use in NIH-initiated clinical trials: The subcommittee recommends classifying the ASUI as a supplemental outcome.

Methods. The ASUI is a retrospective symptom questionnaire consisting of 11 items. Frequency and severity of each symptom (cough, wheezing, dyspnea, and nocturnal awakening) are measured on 4-point Likert scales (for frequency: not at all, 1-3 days, 4-7 days, and 8-14 days during a 14-day period; for severity: mild, moderate, and severe). Two items address the frequency and severity of medication side effects. One open-ended item also is included in the measure, asking patients to list adverse effects of asthma treatment. Responses to this item serve as qualitative anchors for the 2 items addressing frequency and severity of side effects but do not contribute to the scoring of the ASUI.

The method used to develop the ASUI consisted of both qualitative and quantitative analyses. Qualitative analyses were used to choose the symptoms included in the instrument. These methods consisted of a literature review, patient in-depth interviews, and physician interviews about the most common symptoms they saw in their practices. Patients were asked to rank the symptoms they experienced in order of importance according to the effect of the symptoms on their functioning and their well-being. Based on content analyses of these interviews, the 4 core symptoms were chosen.

Quantitative analyses included testing the validity of the instrument for convergent and construct validity using a cross-sectional design with a 2-week reproducibility assessment. At the time of their regular appointments, adults receiving treatment for asthma in a clinical center were invited to participate in the study; 161 agreed.

The ATS/ERS statement does not include a discussion of the ASUI.[6] When discussing symptom measures, the ATS/ERS statement recommends measures that relate to asthma control (versus severity), such as SFDs, SABA use, prebronchodilator and postbronchodilator FEV_1, composite scores, QOL, and treatment side effects related to medication. With the exception of the latter measure, the ASUI does not fit any of these recommendations because it measures frequency and severity of asthma symptoms (coughing, wheezing, and shortness of breath), nighttime awakenings, and the nature, frequency, and severity of medication side effects. Nevertheless, the ASUI can be used as an important tool in clinical trials as a secondary outcome measure to assess the effectiveness of the intervention in reducing common and bothersome symptoms. In addition, it offers an alternative for researchers who do not want to use daily symptom diaries because of concerns about the burden that these tools create for study participants.

The ASUI has unique characteristics that distinguish it from other instruments that combine various symptom measures, such as SFDs. First, contrary to most asthma symptom measures, the psychometric properties of ASUI are well documented and support the reliability and validity of the scale. Second, it is sensitive to change in level of severity. Whereas a patient with severe asthma might not appear to improve according to the instrument in terms of having significant SFDs, he or she might improve in severity and/or frequency of the symptoms, something that is not captured by SFD scales. Certain symptoms are also likely to be more troublesome than others to patients and certain treatments might be more or less desirable: The ASUI captures this information, whereas other scales do not. The scale is also ideal as a cost-effective analysis that requires a condition-specific utility index.

The ASUI has been used in multiple clinical trials[19-39] and appears to be the symptom scale most frequently quoted and used in the literature.

Range of values and scoring. The ASUI score is calculated as the product of 5 utility functions, 4 representing symptoms and 1 representing medication side effects. The side effects function is an open-ended item that does not contribute to the overall ASUI scoring. The 4 symptom functions are cough, wheeze, shortness of breath, and awakening at night. For each symptom function, a numeric value is estimated for each of 10 severity/frequency levels based on patient preferences. Scores range from 1 (no symptoms) to 0, which is the worst score. Thus a decrease in ASUI scores indicates that asthma symptoms' frequency, severity, or both have worsened. To score the instrument, researchers need to refer to a table of utilities provided in the published article by Revicki et al.[1]

Internal consistency and test-retest reliability. No information regarding internal consistency was provided. The ICC for the 2-week reproducibility of the ASUI was 0.74. In addition, the mean values of the ASUI at the 2 times were not significantly different.

Validity. The convergent validity or correlation of the scale with other measures of the same or similar nature was assessed by comparing the ASUI with 2 symptom severity measures: the Physician Severity Rating Scale (PSRS) and the Asthma Disease Severity Scale (ADSS). Both scales were previously found to be reliable and valid in determining asthma severity. The PSRS is a physician global assessment of the severity of asthma on a scale of 1 (mild) to 6 (severe) based on the patient's pulmonary function tests and medical and symptom history information from the asthma medical history instrument[1] component of the PSRS. The ADSS is a composite of resource use, spirometry, and symptoms, including ED visits during the past 12 months ($\geq$1), hospitalizations during the past 12 months ($\geq$1), FEV_1 percent predicted of less than 70%, chronic cough or chronic phlegm, chronic wheeze, chronic breathlessness, and chronic nighttime symptoms. The ASUI scale discriminated well across severity levels using the PSRS ($P < .0001$) and the ADSS ($P < .001$) as comparisons.

Construct validity was assessed by comparing the ASUI with lung functioning, the Health Utilities Index, and Juniper's Asthma Quality of Life Questionnaire.[1] The results of the comparison with lung function (construct validity) showed significant association between ASUI severity scores and FEV_1 percent predicted ($r = 0.27$, $P < .01$) and FEV_1/forced vital capacity ($r = 0.27$, $P < .001$). The ASUI was significantly correlated with the

Health Utilities Index ($r = 0.32$, $P < .001$). There were also strong correlations between the ASUI and the overall score of the Asthma Quality of Life Questionnaire (0.77), the activity limitations score (0.59), symptoms (0.85), emotional function (0.63), and environmental exposure (0.70).

Responsiveness. The ASUI has been used in several randomized controlled trials, such as the Safety of Inactivated Influenza Vaccine in Asthma in Adults and Children (SIIVA)[37] and the Effectiveness of Low-Dose Theophylline as Add-On Treatment in Asthma (LODO) trials,[22] which compared the efficacy of theophylline, montelukast, and placebo in participants with mild to moderate asthma. In addition, several other randomized controlled trials[19,21-23,38] have used the ASUI. In all of these trials, the ASUI was used as a secondary outcome, together with other measures such as QOL and SFDs. The ASUI performed in the expected direction in the majority of these studies and reflected the findings of the other validated outcome measures used in the studies.

The instrument is sensitive to change in severity levels. However, the clinical significance of changes or differences in the scores produced by the instrument is difficult to interpret. For example, it is difficult for clinicians and researchers to interpret the clinical significance of changes or differences in scores from 0.06 to 0.04.[38] As a result, most studies just report that a significant (or no significant) difference was found in ASUI scores or do not discuss the ASUI scores at all. This observation, as well as the complexity of the scoring system, may constitute the most important limitations of the instrument.

Practicality and risk. Because it contains only 11 items, the scale is easy to administer at minimal cost for researchers and clinicians. Training for administration is also minimal, although training on the scoring system is required because it is more complicated than other scales. It has limited use for clinical care because of the complexity of calculating an ASUI score. To date, a minimal clinically important difference value has not been determined.

The generalizability of the scale is also unclear. The scale's construction is based on weights assigned to different preferences that might not be generalizable to other groups. The participants in the study used to validate the scale had the following demographic characteristics: mean age (±SD) of 34.7 ± 10.7 years; 59% female, 79% white, 17% black, and 3% Asian American. ASUI scores were unrelated to age (in adults), sex, and educational level. The scale has been validated only for adults; no pediatric analogue exists. In addition, evidence exists that the algorithms used to score the ASUI would need to be modified for each racial/ethnic group. The results of the international validation of the scale in Italy, France, and the United Kingdom showed variability in the scores across countries, particularly for medication side effects.[25] Variability also was observed in the rank order of the multisymptom states. Differences were identified across countries in deriving ASUI weighting algorithms, which are necessary to develop the table of scores used to arrive at an overall score. When the combined data (from all countries) were analyzed, the authors were able to fit the multiplicative multiattribute utility function and derive ASUI scores based on the algorithm. However, a new algorithm had to be derived for each country because of cross-national differences (especially in France and Italy) in the relative importance or value placed on the same symptoms. Differences were particularly evident regarding the severe wheeze state and the moderate level multisymptom states (involving cough and wheeze or dyspnea). US participants tended to rate these symptom states as more severe than did those from Italy and France, whereas United Kingdom participants fell in the middle. The authors recommended that the stability of the weights used for the scoring algorithms be tested in future studies for SES and culture.

ADDITIONAL CONSIDERATIONS

Electronic diaries

Patient-reported daily diaries provide the opportunity to collect real-time information about respiratory symptoms, SABA use, and other information. Compared with interval questionnaires at study visits (which are based on retrospective assessments over the previous 1 to 4 weeks or more), daily diaries are theoretically less susceptible to problems related to incomplete recall and/or recall bias.[40] However, diary data are often incomplete, and results of studies indicate that diaries are often not completed in real time and are susceptible to data fabrication.[41] Such problems are not limited to the use of diaries to assess asthma symptoms but have been observed for other conditions as well.[42] These concerns about the use of paper and pencil–completed diaries have led to the development of electronic daily diaries that can time- and date-stamp entries, as well as promote timely completion and adherence via devices, such as reminders and restricted data entry times.[4,43] The disadvantages of electronic diaries include the costs of handheld devices (as high as hundreds of dollars per unit), the need for user-friendly interfaces for data entry and download, equipment malfunction, and availability and adequacy of technical support. Because evidence is insufficient to indicate that daily diary data are superior to interval questionnaires[44] and because of potential disadvantages of electronic diaries compared with paper-and-pencil versions of daily diaries, we do not advocate their routine use in studies of asthma at the present time. Decisions regarding the use of electronic diaries should be made by investigators in light of the research objectives and resources available to complete the studies.

SYMPTOM DERIVATIVES

SFDs

Derivatives of daily symptom diary data, such as SFDs, can be used to compare relative symptom frequency in study participants by reporting the number or proportion of days without asthma symptoms for each study group. However, various investigators have measured SFDs using different instruments in studies of adults (eg, Daily Symptom Diary Scale and Nocturnal Diary Scale,[45] the Symptom-Free Day Questionnaire,[38] and Daily Diary[46]) and children (eg, PACD[3]). Moreover, as discussed in the ATS/ERS statement, SFDs may be insensitive to change due to floor and ceiling effects in participants with mild and severe asthma, respectively. Because there is no consensus about how to measure SFDs and the psychometric properties of measuring SFDs are unclear, the subcommittee recommends SFDs as an emerging outcome measure.

Symptoms as a component of composite indices

A variety of indices have been used in clinical trials that include symptoms as 1 component of a larger index, such as *episode-free days*,[18,47] *asthma control days*,[13,48] and *maximum symptom*

days[49] or *asthma control*.[50,51] These indices record not only symptom frequency and/or severity but also may record events such as lost sleep, changes in activities of daily living, inpatient admissions, and ED and clinic visits, among others, as well as evaluating lung function (eg, peak expiratory flow). Thus symptoms are recorded as part of a more global composite index that is used to evaluate asthma control and response to therapy. These indices have varying degrees of validation (see the "Composite scores of asthma control" article). When symptom scores are measured in these ways, it is not possible to disentangle their individual value from that of the entire index as an outcome measure. Research is needed to compare the value of measuring symptoms alone to symptoms as a part of a composite index.

Another complication of measuring asthma symptoms is the interrelationship between symptoms and level of treatment. For example, 2 patients with asthma may have the same symptom score, but 1 may be taking high doses of medication and the other minimal or no medication. Thus the symptom score alone does not capture the dimension of symptoms in the context of underlying asthma severity and the treatment taken that results in the reported level of symptoms. In an effort to address the relationship of asthma symptoms and medication use, the investigators of the Inner-City Asthma Consortium developed and validated an instrument to capture symptoms in the context of asthma severity and control. The instrument includes items on exacerbations (systemic corticosteroid use), urgent care use, and pulmonary function. Preliminary data from a randomized treatment trial show this measure to be more sensitive to treatment effects than is any single measure alone.[52] The tool could potentially be used with individuals of all ages and races, but it has only been validated so far in children and adolescents of low SES.

The effort to combine assessment of several factors that relate to symptom levels is not dissimilar to the effort to combine measures to identify the level of asthma control. Future evaluations are needed to determine whether these different composite instruments (burden and control) provide unique or comparable assessments.

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Asthma outcomes: Exacerbations

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Background: The goals of asthma treatment include preventing recurrent exacerbations. Yet there is no consensus about the terminology for describing or defining "exacerbation" or about how to characterize an episode's severity.
Objective: National Institutes of Health institutes and other federal agencies convened an expert group to propose how asthma exacerbation should be assessed as a standardized asthma outcome in future asthma clinical research studies.
Methods: We used comprehensive literature reviews and expert opinion to compile a list of asthma exacerbation outcomes and classified them as either core (required in future studies), supplemental (used according to study aims and standardized), or emerging (requiring validation and standardization). This work was discussed at a National Institutes of Health–organized workshop in March 2010 and finalized in September 2011.
Results: No dominant definition of "exacerbation" was found. The most widely used definitions included 3 components, all related to treatment, rather than symptoms: (1) systemic use of corticosteroids, (2) asthma-specific emergency department visits or hospitalizations, and (3) use of short-acting β-agonists as quick-relief (sometimes referred to as "rescue" or "reliever") medications.
Conclusions: The working group participants propose that the definition of "asthma exacerbation" be "a worsening of asthma requiring the use of systemic corticosteroids to prevent a serious outcome." As core outcomes, they propose inclusion and separate reporting of several essential variables of an exacerbation. Furthermore, they propose the development of a standardized, component-based definition of "exacerbation" with clear thresholds of severity for each component. (J Allergy Clin Immunol 2012;129:S34-48.)

Key words: *Asthma exacerbations, severity of acute asthma, systemic steroids in asthma, urgent asthma care*

Abbreviations used
ATS: American Thoracic Society
ED: Emergency department
EPR-3: Expert Panel Report 3
ERS: European Respiratory Society
FENO: Fractional exhaled nitric oxide
GINA: Global Initiative for Asthma
ICU: Intensive care unit
NHLBI: National Heart, Lung, and Blood Institute
NIH: National Institutes of Health
PEF: Peak expiratory flow
SABA: Short-acting β-agonist
SES: Socioeconomic status
UC: Urgent care

Asthma clinical research lacks adequate outcomes standardization. As a result, our ability to examine and compare outcomes across clinical trials and clinical studies, interpret evaluations of new and available therapeutic modalities for this disease at a scale larger than a single trial, and pool data for observational studies (eg, genetics, genomics, and pharmacoeconomics) is impaired.[7] Several National Institutes of Health (NIH) institutes that support asthma research (the National Heart, Lung, and Blood Institute [NHLBI]; National Institute of Allergy and Infectious Diseases; National Institute of Environmental Health Sciences; and Eunice Kennedy Shriver National Institute of Child Health and Human Development), as well as the Agency for Healthcare Research and Quality, have agreed to an effort for outcomes standardization. This effort aims at (1) establishing standard definitions and data

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TABLE I. Recommendations for classifying asthma exacerbation outcome measures for NIH-initiated clinical research in adult (≥18 years of age) and adolescent (12-17 years of age) populations

	Characterization of study population for prospective clinical trials (ie, baseline information)	Prospective clinical trial efficacy/effectiveness outcomes	Observational study outcomes*
Core outcomes	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)
Supplemental outcomes	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
Emerging outcomes	1. Biomarkers of exacerbation (FENO, sputum markers, exhaled breath condensate analytes) 2. For trials in the acute management of exacerbations (ED setting): SABA response	1. Stratification of exacerbations by severity 2. Short course of high-dose inhaled corticosteroids as a definition of an asthma exacerbation 3. SABA use (with a predefined cutoff value) as a definition of an asthma exacerbation 4. Biomarkers of exacerbation (FENO, sputum markers, exhaled breath condensate analytes) 5. Total dose and duration of systemic corticosteroid use	None
Call for new outcome measures/instruments	1. Component-based definition of "exacerbation" with threshold values for each component 2. A standard format for characterizing an exacerbation by precipitating factor (eg, viral illness, allergen exposure, pollutant exposure, medication nonadherence) 3. A standard format to define factors that contribute to the decision to use systemic corticosteroids or seek UC		

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

TABLE II. Key points and recommendations for adult and adolescent populations

1. Recommended definition: **An exacerbation is a worsening of asthma requiring the use of systemic corticosteroids (or for patients on a stable maintenance dose, an increase in the use of systemic corticosteroids) to prevent a serious outcome.**
2. Tremendous variation exists in the literature regarding the terminology for an asthma exacerbation. We identified 15 different terms in use to refer to an asthma exacerbation, which makes comparison across studies problematic. An asthma exacerbation is rarely defined by a single diagnostic component, but when it is, treatment with systemic corticosteroids is the one most commonly used. Variation in the way subjects with asthma present supports the use of a definition that includes multiple components, yet little evidence exists to support a specific set of components or the thresholds for any individual component within a given definition.
3. We found no consistent or dominant definition of "asthma exacerbation" in the literature. Most commonly, the definition for "exacerbation" in adults who have asthma was based on 3 criteria: (1) the use of systemic corticosteroids, (2) healthcare utilization that included an ED or UC visit or hospitalization; and (3) the use of SABAs as quick relief (sometimes referred to as "rescue" or "reliever") medication (with or without concurrent reference to asthma symptoms).
4. Variation exists in the way the severity of an exacerbation is classified. Most studies do not distinguish levels of severity. When exacerbations are noted as "severe," the definition typically includes initiation of systemic corticosteroid treatment and/or a measure of ED or UC utilization or hospital admission.
5. The ability to distinguish between poorly controlled asthma and an exacerbation is difficult and is characterized by vague and inconsistent terminology.
6. Standardized terminology, definition of severity levels, and precise operational definitions of the components that are used to identify an exacerbation are needed.
7. Currently, biomarkers are not useful in defining an exacerbation. However, they may be useful in better understanding the biology and mechanisms of exacerbation and in defining the population at risk for it.

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) identifying promising outcome measures for asthma clinical research that require further development. In the context of this effort, 7 expert subcommittees were established to propose and define outcomes under 3 categories—core, supplemental, and emerging:

TABLE III. Recommendations for classifying asthma exacerbation outcome measures for NIH-initiated clinical research in pediatric populations (0-4 and 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*
Core outcomes	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)
Supplemental outcomes	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	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)	None
Emerging outcomes	1. Biomarkers of exacerbation (FENO, sputum markers, exhaled breath condensate analytes†)	1. Stratification of exacerbations by severity 2. Short course of high-dose inhaled corticosteroids as a definition of an asthma exacerbation 3. SABA use (with a predefined cutoff value) as a definition of an asthma exacerbation 4. Biomarkers of exacerbation (FENO, sputum markers, exhaled breath condensate analytes†) 5. Total dose and duration of systemic corticosteroid use	None
Call for new outcome measures/instruments	1. Component-based definition of "exacerbations" with threshold values for each component 2. A standard format for characterizing an exacerbation by precipitating factor (eg, viral illness, allergen exposure, pollutant exposure, medication nonadherence) 3. A standard format to define factors that contribute to the decision to use systemic corticosteroids or seek UC		

ASS, Asthma Severity Score[1]; *CAS,* Clinical Asthma Score[2]; *PASS,* Pediatric Asthma Severity Score[3]; *PI,* Pulmonary Index[4]; *PRAM,* Preschool Respiratory Assessment Measure[5]; *PS,* Pulmonary Score.[6]

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

†In older children who can perform these techniques.

TABLE IV. Key points and recommendations for pediatric populations

1. Recommended definition: **An exacerbation is a worsening of asthma requiring the use of systemic corticosteroids (or for patients on a stable maintenance dose, an increase in the use of systemic corticosteroids) to prevent a serious outcome.** This definition is the same for pediatric (aged 0-4 and 5-11 years) as for adult and adolescent populations. Although the use of SABAs is a more commonly used criterion or factor for defining "exacerbation" in children, the threshold criterion for distinguishing between loss of control and an asthma exacerbation has not been defined. Therefore this criterion could not be included as a core outcome.
2. Asthma exacerbations in children aged 0-4 years are particularly difficult to identify for several reasons. Foremost is the consideration that the differentiation between changes in daily symptoms and a potential cluster of symptoms sufficient to be termed an exacerbation is based on the caregiver's perception of symptoms and not the child's perception. The threshold for symptom identification and initiation of therapy depends on the education level and personality of the caregiver.
3. Currently, biomarkers are not useful in defining "exacerbation." However, for older children (aged 5-11 years), biomarkers may be useful in better understanding the biology and mechanisms of exacerbation and in identifying the population at risk for exacerbation.
4. Many physiologic measures (ie, FEV_1) and biomarker techniques (FENO, induced sputum, and exhaled breath condensate) are age dependent and difficult to use reliably in young children.

- *Core outcomes* are identified as a selective set of asthma outcomes to be considered by participating NIH institutes and other federal agencies as requirements for institute/ agency-initiated funding of clinical trials and large observational studies in asthma.
- *Supplemental outcomes* are asthma outcomes for which standard definitions can or have been developed, methods for measurement can be specified, and validity has been proved but whose inclusion in funded clinical asthma research will be optional.

TABLE V. Methods for reporting core and supplemental outcome measures for asthma exacerbations for all ages

For all outcome measures	Report outcomes by: 1. Events for total study population 2. Events occurring by age groups (as applicable to study): A. 0-4 years B. 5-11 years C. 12-17 years D. 18-64 years E. 65 years and older
Exacerbations	Preferred: 1. Overall rate (number of events requiring systemic corticosteroids/participant/time interval specified by study). Annual rates are preferred for studies of at least 12-month duration. Annualization for shorter studies is not recommended. 2. Weighted mean rate (total exacerbations in the study group/total person time in the group) Additional: 1. Time to first exacerbation 2. Percentage of study group with an exacerbation 3. Total corticosteroid dose (mg/patient/unit of time and duration of treatment)
Utilization events (ED or UC visits, hospitalizations, ICU admissions, intubations)	No. of events/participant/year Percentage of study group with an event
Deaths (asthma specific and all cause)	Percentage of study group with an event
Validated assessment measures for studies in acute-care settings	Methods: PASS, PS, PRAM, CAS, PI, ASS, symptom scores (see text); reported as defined by the scores used in the measure

ASS, Asthma Severity Score[1]; *CAS,* Clinical Asthma Score[2]; *PASS,* Pediatric Asthma Severity Score[3]; *PI,* Pulmonary Index[4]; *PRAM,* Preschool Respiratory Assessment Measure[5]; *PS,* Pulmonary Score.[6]

- *Emerging outcomes* are asthma outcomes that have the potential to (1) expand and/or improve current aspects of disease monitoring and (2) improve translation of basic and animal model–based asthma research into clinical research. Emerging outcomes may be new or may have been previously used in asthma clinical research, but they are not yet standardized and require further development and validation.

Each subcommittee used the recently published *American Thoracic Society (ATS)/European Respiratory Society (ERS) Statement: Asthma Control and Exacerbations—Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice*[8] (hereafter referred to as the ATS/ERS statement) as a starting point and updated, expanded, or modified its recommendations as the subcommittee deemed appropriate. Each subcommittee produced a report that was discussed, modified, and adopted by the Asthma Outcomes Workshop that took place in Bethesda, Md, on March 15 and 16, 2010. The reports were revised accordingly and finalized in September 2011. The workshop's recommendations in regard to asthma exacerbation outcomes are presented in this article and are summarized in Tables I through V.[1-6]

International guidelines consistently describe the goals of asthma treatment to include the control of patients' current symptoms and the prevention of recurrent exacerbations. Several definitions of an asthma exacerbation and exacerbation severity have been put forth by various groups, including the Global Initiative for Asthma (GINA),[9] the NHLBI/National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3),[10] and the ATS/ERS statement. According to EPR-3, "asthma exacerbations are acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, and chest tightness—or some combination of these symptoms." Exacerbations are characterized by decreases in expiratory airflow that can be documented and quantified by simple measurement of lung function (spirometry or peak expiratory flow [PEF]).

The GINA guidelines define "acute exacerbations" (asthma attacks or acute asthma) as "episodes of progressive increase in shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms, accompanied by decreases in expiratory airflow that can be quantified by measurement of lung function." These guidelines also define exacerbations as acute and severe loss of control that requires urgent treatment. The GINA guidelines refer to the severity of exacerbations but do not define exact criteria by which to distinguish severity levels.

The recently published ATS/ERS statement on the standardization of outcomes defined "exacerbations" as "events characterized by a change from the patient's previous status." The task force stratified its definition by severity:

- Severe asthma exacerbations are events that require urgent action on the part of the patient and physician to prevent a serious 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 systemic corticosteroids (tablets, suspension, or injection) 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.
  - B. A hospitalization or emergency department (ED) visit because of asthma requiring systemic corticosteroids.
- Moderate asthma exacerbations are events that should result in a temporary change in treatment in an effort to prevent the exacerbation from becoming severe. A moderate

exacerbation should include 1 or more of the following: deterioration in symptoms, deterioration in lung function, and increased use of short-acting β-agonist (SABA) bronchodilator. These features should last for 2 days or more but not be severe enough to warrant systemic corticosteroid use and/or hospitalization or ED visits for asthma.

The Asthma Exacerbations Subcommittee identified definitions of exacerbations through literature searches, review of documentation from phase III clinical trials (for both adults and children) registered on clinicaltrials.gov, and published reports from National Institute of Allergy and Infectious Diseases and NHLBI clinical research networks. The search identified 27 pediatric citations (including 2 study design papers),[11-37] 47 adult study citations,[38-82] and 11 articles related to specific exacerbation measures. Excluding studies that did not clearly focus on exacerbation, a total of 65 studies (34 phase III and 31 NIH consortia studies) were included in this review.

In developing its recommendations, the subcommittee conducted independent reviews for pediatric and adult populations. Further distinctions within the adult and pediatric groups also need to be made because the clinical interpretation of significance of an exacerbation may be different for various age groups. Our report discusses in more detail issues unique to children aged 0-4 years and children aged 5-11 years.

Outcomes for children aged 12 years and older tended to be aggregated with adult outcomes in the literature, making specific conclusions for adolescent populations more difficult. Therefore recommendations for adolescents (aged 12-17 years) are incorporated within the adult recommendations. However, further work studying adolescents, an age group that is developmentally distinct from older and younger ones, is important[83]), and we encourage reporting of outcomes by age groups that separate adolescents from adults (age 12-17 years and ≥18 years).

Similarly, older adults with asthma (aged ≥65 years) present unique diagnostic and management issues.[84] Older adult patients have more difficulty using inhalers, peak flow meters, and undergoing spirometry because of physical (eg, arthritis, visual) and cognitive impairments and memory issues.[85-88] The diagnosis of exacerbations is also more complicated in this population, given poor perception of symptoms, reduced expectations with regard to activity level, and an increased risk of adverse effects from medications. The subcommittee recommends that exacerbation outcomes in this age group also should be reported separately. Given the paucity of data for this population, this approach will help in the development of a database that will guide future asthma exacerbations research in older adults.

ASTHMA EXACERBATIONS AS AN OUTCOME MEASURE

Definition and methodology for measurement

Almost no 2 studies define "asthma exacerbation" in the same way. The most commonly included exacerbation outcomes were the need for systemic corticosteroids, urgent unscheduled care, specifically ED or urgent care (UC) visits, and hospitalizations for asthma.

The subcommittee proposes the following definition, primarily based on the ATS/ERS statement: **"An exacerbation is a worsening of asthma requiring the use of systemic corticosteroids (or for patients on a stable maintenance dose, an increase in the use of systemic corticosteroids) to prevent a serious outcome."** The term "exacerbation" should be distinguished from the terms "not well-controlled asthma" or "uncontrolled asthma," which are measures of chronic disease activity (see the "Asthma Outcomes: Composite scores of asthma control" article in this supplement).

Core outcome measures for exacerbations

The above definition does not include detailed aspects of an asthma exacerbation that describe levels of severity, characterize the nature of the exacerbation, or relate to its outcome. However, information on the range of events associated with an exacerbation, such as an ED or UC visit, a hospitalization, an intensive care unit (ICU) stay, intubation, or death, should be outlined. Each type of event has unique biases that affect the rate observed in different healthcare settings and populations. Inclusion of all events under a combined outcome definition is possible, but information on the occurrence of each type of event should always be provided to allow for more in-depth analysis and for better comparisons between independent trials or studies. Therefore the subcommittee recommends that the core exacerbation outcomes that need to be reported in all asthma clinical trials and in all age groups are the following:

1. all worsening asthma events in which systemic corticosteroids were initiated or increased to prevent a serious outcome, including use of systemic corticosteroids in association with any form of healthcare provider encounter;
2. all asthma-specific ED or UC visits that involved treatment with systemic corticosteroids;
3. all asthma-specific hospitalizations that involved treatment with systemic corticosteroids;
4. all asthma-specific ICU admissions or intubations; and
5. all deaths (all cause and asthma related).

We agree with the ATS/ERS statement definition requiring 3 days of systemic corticosteroids for an event to qualify as an exacerbation in adult/adolescent populations. Three days, as the lower limit of the recommended duration of treatment, is also based on the EPR-3 guidelines. In the pediatric population we do not include the requirement for 3 days of systemic corticosteroids to define an event as an exacerbation because evidence in pediatric acute care supports the use of only 1 to 2 days of dexamethasone to achieve better adherence and similar outcomes.[89-91] The literature on the use of 1 to 2 days of dexamethasone in the treatment of exacerbations is limited to pediatric populations, and the requirement for 3 days of systemic corticosteroids among adults is recommended until this practice has been evaluated in adolescent/adult populations. We further propose that the total corticosteroid dose used in the treatment of an exacerbation (milligrams/patient/unit of time and duration of treatment) be reported as an attribute of the severity of an exacerbation.

The subcommittee's recommendations, with respect to core outcomes, also differ from the ATS/ERS statement in the following areas:

- The subcommittee does not endorse severity stratification in the core outcome definition. There is not a validated

way to define the lower threshold of moderate exacerbations and to distinguish a moderate exacerbation from loss of chronic asthma control. Therefore severity stratification is not recommended as a core outcome. In addition, possible confusion between the use of severity to describe the underlying severity of disease, as opposed to the severity of exacerbations, can arise. Furthermore, severity of an exacerbation can refer to 2 distinct phenomena: (1) the intensity of symptoms in general or (2) the magnitude of individual features, such as the severity of airway obstruction. If a gradation of exacerbations is to be utilized, the terminology needs to be unambiguous.

- The subcommittee recommends that exacerbation outcomes within the adult population be reported separately for adolescents (aged 12-17 years) and older adults (aged ≥65 years of age).
- The subcommittee recommends separate reporting of deaths. There is debate over whether all-cause mortality or asthma-specific mortality is the more appropriate outcome to measure in asthma clinical trials. The validity of disease-specific mortality as an outcome rests on the assumption that the cause of death can be accurately determined and documented. This assumption has been challenged by studies that evaluate the accuracy of death certificates.[92,93] In contrast, all-cause mortality does not rely on assumptions regarding the cause of death and will capture deaths, including unexpected fatal side effects of medical care. All-cause mortality as an outcome measure has been increasingly used in clinical trials.[94,95] Therefore the subcommittee recommends that both all-cause and asthma-specific mortality be reported.

Exacerbation outcomes are commonly reported in several ways, with multiple measures and multiple denominators used within a given study. Time to first event and rate of occurrence (number per patient per time interval) are the most frequently used methods of measuring exacerbations. The ATS/ERS statement recommends the use of both these methods. Analysis of time to first exacerbation minimizes the effect of differential dropout and of individual subjects with multiple exacerbations. However, analysis of the rate of exacerbations (reported as "number/patient/year") is the most useful method for comparing patient populations. Other potential methods include the number of exacerbations and the percentage of the population with an event.

The subcommittee recommends reporting exacerbations as the rate of events per participant per year in all asthma clinical trials for both adult and pediatric populations. The preferred method for reporting the rate is the weighted mean rate, which is obtained by pooling all the exacerbation events in a given treatment group of a trial and dividing by the total person-time in that group. In addition to the overall exacerbation rate, the subcommittee recommends that the rate of the individual types of events described above (ie, ED or UC visits, hospitalizations, ICU admissions or intubations, and deaths) also be reported independently to allow comparison between studies. It is important to emphasize that drawing inferences from summary statistics between groups can be problematic because event count distributions are often skewed and have a large proportion of zeros. Sample size and data distribution should be evaluated to ensure that appropriate analysis measures are used.[96,97] Providing the median and the interquartile range of count data, in addition to reporting the mean, gives greater insight into data distribution.[98]

Core measures to characterize study populations

Exacerbations constitute a distinct and important clinical characteristic of asthma, and the prior history of exacerbations should be regarded as a core outcome in the description of the population that participates in a clinical trial or an observational study of asthma. The history of an exacerbation in the prior 12 months is 1 of the strongest predictors of future exacerbations.[99-102] Lieu et al[103] observed that having filled a prescription for a systemic corticosteroid or having had a hospitalization during the prior 6 months was associated with increased risk of future admission for asthma. The history of past exacerbation can be easily and reliably obtained, especially when defined as an event requiring the use of systemic corticosteroids, an ED or UC visit, or a hospitalization.

Supplemental measures to characterize asthma exacerbations in acute-care setting studies

Standardizing the characterization of exacerbations for acute intervention trials in the ED, UC, or hospital setting (as opposed to the use of exacerbations to characterize a population) was not the focus of the subcommittee's work. However, national guidelines recommend objective measures of lung function to accurately assess the level of airway obstruction. FEV_1 is used to categorize the severity of an exacerbation for clinical trials that focus on the acute management of these events. For this reason, the subcommittee has included FEV_1 as a supplemental outcome for characterizing the severity of acute asthma exacerbations in acute intervention trials in adolescent and adult populations. In addition, the subcommittee considers the FEV_1 response to SABAs as an emerging outcome for subject characterization of adults and adolescents in acute-care setting studies. FEV_1 or other lung function measures are frequently difficult to obtain in young children, especially in the setting of an acute exacerbation. Several clinical scores have been developed and validated for use in the clinical management of acute exacerbations.[1-6] These measures may have a role in clinical research focused on the ED setting and on characterization of subjects potentially enrolled in studies. The subcommittee recommends these instruments as supplemental outcomes for this type of study. These measures have not been validated in adolescent or adult populations, and therefore have not been included for the older age groups.

Medical and scientific value

Management and prevention of asthma exacerbations is a key focus of asthma care, patient action plans, and the Healthy People 2010 objectives. Exacerbations can be life-threatening and can result in costly utilization of emergency care: Between 35% and 50% of medical expenditures for asthma have been attributed to acute exacerbations.[104] A definition of exacerbation that includes an intervention, such as the use of systemic corticosteroids, an ED or UC visit, or a hospitalization, has clinical relevance and, as noted in the ATS/ERS statement, is "intuitively valid." The frequency of exacerbations requiring intervention with systemic corticosteroids has been correlated in observational studies with the designation of persistent, rather than intermittent, asthma[105,106]

and is 1 of the central components distinguishing intermittent from persistent asthma in the EPR-3 guidelines.

Reliability

The validity of a measure of an exacerbation cannot be judged by repeatability since an exacerbation, unlike a given biomarker, cannot be measured twice within a short period of time to assess its variability. Both systemic corticosteroid use (initiated by patient or clinician) and an ED or UC visit or a hospitalization require an assessment by the patient and/or clinician that the event is severe enough to warrant intervention. However, the decision to intervene depends on the patient's perception and the provider's judgment, with remarkable variation across populations and healthcare settings.[107] The decision to use systemic corticosteroids may take into account patient or provider experience with side effects. This may be particularly important for patients who have previously experienced mood disturbance with oral systemic corticosteroids.[108,109] To gather information on the thresholds that warrant intervention, the subcommittee recommends that prospective studies clearly describe the parameters used in the decision to intervene (systemic corticosteroids [oral and intravenous], ED or UC visits, and hospitalizations). Similarly, the factors (clinical, psychological, and contextual) that contribute to patient and clinician decisions to use systemic corticosteroids or that prompt UC utilization need to be further investigated. Future research can focus on development of a checklist or standard format for collection of these data.

Our recommendation for reporting the rate of the individual components—systemic corticosteroids (oral and intravenous), ED or UC visits, and hospitalization—will improve the ability to compare findings across multiple trials. The factors that affect use of systemic corticosteroids are not identical to those that influence the decision to visit the ED or to admit a patient to a given healthcare setting, supporting the recommendation for separate reporting of individual events. Finally, differences in the rate of exacerbations will occur, depending on whether the outcome is obtained by self-report or captured prospectively in a clinical trial and verified by review of records. Prior studies have shown differences in the rate of events depending on how this information was obtained. When patient reports and administrative data were formally compared, hospitalizations had the highest agreement between the 2 data sources (93.9%), with lower values for ED visits (79.8%) and oral systemic corticosteroid bursts (65.7%). The magnitude of the difference increases as the number of events increases.[110]

In reporting the use of systemic corticosteroids, another factor that affects reliability is the lack of quantification of corticosteroid dosage. Clinical trial reports do not always clarify whether the corticosteroid dose was standardized in the protocol or left to physician discretion. The subcommittee recommends that the dosage (milligrams of corticosteroid per participant per unit time) and duration of treatment be included in the standard reporting of asthma exacerbations (Table V). Whether the duration of treatment was prespecified or dependent on the patient's progress and how closely consecutive courses were handled should be described.

Responsiveness

At a group level in clinical trials, use of systemic corticosteroids and healthcare utilization has been found to be responsive to treatment (ie, these measures are expected to decrease with effective interventions).

Validity and associations

The construct validity of our proposed definition of exacerbation is supported by the stipulation that it requires an intervention; the patient and caregiver agree that an intervention is necessary. This suggests a clinically relevant outcome.

There is no gold standard against which to evaluate the criterion validity for any definition of exacerbation. However, multiple clinical trials demonstrate convergent validity with other measures of asthma-related health status.[111-113] In addition, exacerbations are associated with the risk of excess lung function decline in patients with asthma,[114] demonstrating the predictive validity of exacerbations.

Practicality

The use of systemic corticosteroids, an ED or UC visit, and hospitalizations are relatively simple to record and are objective and quantifiable. Data on these events can be easily obtained for both prospective and retrospective analyses. The reporting of the individual components can be easily implemented and thus can be effective in standardizing study results. The issue of discerning use of systemic corticosteroids with ED visits and hospitalizations (especially with claims data), however, can be difficult.

Demographic considerations

Age. As elaborated in the introduction, there are differences in how exacerbations are identified in various age groups. Distinctions between pediatric populations, adolescents (who are developmentally distinct from older and younger individuals), and older adults from younger adults are important to consider. Therefore the subcommittee recommends reporting exacerbations separately for 5 age categories: 0 to 4, 5 to 11, 12 to 17, 18 to 64, and 65 or greater years.

Socioeconomic status and geographic variation. Geographic variation in asthma outcomes has been observed between neighborhoods within a city.[115] These differences are not adequately explained by race/ethnicity or by socioeconomic factors, such as income and insurance status. Differences in access to care, orientation to the healthcare system, and health literacy also play a role. In addition, community characteristics such as poverty, underemployment, limited social capital, substandard housing, and high violence and community-level stress, more commonly encountered in the inner city, have been associated with the risk of asthma exacerbations.[22,116,117] The quality of ambulatory care, including choice of long-term control medication and thresholds for admission, plays a key role in determining geographic differences in hospitalization rates for chronic childhood asthma.[118] Children served by Medicaid tend to use the ED more frequently for asthma services than do privately insured children. Racial/ethnic disparities in readmission rates persist after control for comorbidities, payer type, and income.[119] Racial and economic segregation are particularly striking in the differences between inner-city and suburban populations noted in published asthma exacerbation rates. These differences follow a distinct geographic pattern, with the lowest rates in suburban residents (1.05/1000 child-years), followed by "other urban" (2.99/1000 child-years) and inner-city residents (5.21/1000 child-years).[120]

Therefore it is important to understand the broader societal context in which studies are performed to compare results across studies. A standard composite measure to define socioeconomic status (SES) for characterization of a given study population has

not been defined, but individual components that describe SES are well established. The subcommittee recommends that SES be used as a supplemental outcome for the characterization of study populations but also calls for the development of a consistent methodology for clinical trials to characterize SES and societal context of the population being studied to facilitate comparison across studies. A consensus is needed on which elements to measure, acknowledging that measurement for children may differ from that for adults.

Limitations

As noted, 2 elements recur among the definitions for an asthma exacerbation: (1) use of systemic corticosteroids and (2) a change in asthma health status severe enough to require a visit to the ED or UC facility or a hospital admission. A third element frequently reported in the pediatric literature is the increased frequency of SABA use. However, the threshold criterion for distinguishing loss of asthma control from an asthma exacerbation has not been defined and so cannot be included as a core outcome.

There is an emerging literature examining the use of increased doses of inhaled corticosteroid, rather than systemic corticosteroid, as a method for delivering this class of drug for acute exacerbations. However, randomized trials have failed to show decreased exacerbation rates with doubling the inhaled corticosteroid dose,[121,122] and more recent studies, using a 4-fold increase in inhaled corticosteroid, did not reach statistical significance for the primary study endpoint.[123] Therefore the subcommittee recommends that the use of a short course of high-dose inhaled corticosteroid as a criterion to define an exacerbation can only be considered an emerging outcome. The subcommittee recommends conducting a larger trial examining 4-fold increase in inhaled corticosteroid doses as a response to loss of asthma control.

Another potential limitation centers on the inclusion of UC visits with ED visits in defining an asthma exacerbation. It is recognized that utilization patterns for UC clinics can vary widely across locations (eg, in relation to waiting times in the closest ED) and according to insurance patterns. In some areas a UC clinic can function as an emergency treatment venue, whereas in others the UC visit resembles an outpatient encounter. Conversely, many UC clinics have limited ability to accept underinsured patients, and many of these patients may go to the ED. In sum, accurately differentiating UC visits from ED visits is not possible in many healthcare settings. Therefore the subcommittee recommends combining UC and ED visits in both the definition and reporting of asthma exacerbations. The subcommittee concludes that the use of systemic corticosteroids should be the defining criterion, regardless of venue of care.

Finally, accurately determining when asthma-related hospitalization or ED visits are associated with the use of systemic corticosteroids can be difficult. While the recommended definition of an asthma exacerbation includes an asthma-related hospitalization or ED visit requiring systemic corticosteroids, in some studies it will not be possible to distinguish the healthcare utilization events that include the use of systemic corticosteroids from those events that do not.

Priority for NIH-initiated clinical research

The subcommittee acknowledges that there is no fully validated definition of an asthma exacerbation. However, our recommended definition contains central elements of the EPR-3 guidelines and the ATS/ERS statement and is quantifiable and objective. The methods for measuring and reporting are the most standardized. Multiple clinical trials have used this definition of "exacerbation" as an outcome; evaluation of exacerbations, using this definition with other measures of asthma health status, has demonstrated concurrent validity. As an example, an analysis of a large, longitudinal study of children confirmed a relationship between the severity of airflow obstruction and the risk of exacerbations.[105] In addition, at a group level, the use of systemic corticosteroids and/or UC utilization has been found to be responsive to treatment.

The proposed definition is clinically relevant and has significant scientific value. The rate of exacerbations, as defined, has analytic properties that allow easy comparison. Reliability of the definition has limitations when used in retrospective analyses; however, in prospective trials the definition can be operationalized to promote its consistency among studies. The proposed definition has been shown to be responsive to treatment with both pharmacologic and nonpharmacologic interventions. Although there is no gold standard by which to assess its criterion validity, there is evidence for construct and predictive validity. Furthermore, it is a measure that is practical and relatively easy to record. Issues related to culture, SES, access to care, and differences in healthcare systems may affect its value, but the study methods and procedures within prospective trials can help account for these effects.

FUTURE DIRECTIONS AND RESEARCH QUESTIONS

A component-based definition of "asthma exacerbation"

Many definitions of "asthma exacerbation" combine multiple components, such as change in symptoms, lung function, and SABA use. The subcommittee believes that this approach should be pursued with the goal of developing and validating a standard, component-based definition. There has been increasing awareness of heterogeneity of the underlying disease processes in asthma. Recent reports have highlighted the importance of different asthma phenotypes and their natural history.[124-129] As these phenotypes may alter the way individual patients present and how they respond to intervention, characterization of patients' phenotypes will become increasingly important in the development of targeted therapies. Even in patients with well-characterized asthma, the relationship between the underlying disease processes and their clinical manifestations is not strong. At a group level, pathophysiologic markers, such as sputum eosinophils and airway hyperresponsiveness, do not necessarily correlate strongly with one another or with patients' clinical features.[130] This lack of correlation suggests that each component adds independent information about a patient's underlying phenotype and highlights 2 challenges: how to assess patients with asthma and how to judge treatment response. In clinical trials, a wide array of outcome measures has been used to evaluate asthma. Yet there has been no agreement on the relative importance or weight of any of these measures. Therefore reaching consensus about the components that should be included in the definition of exacerbation is a question worthy of further investigation.

We discuss each of the following possible components of a future component-based definition of asthma exacerbations in

more detail below: symptoms, SABA use, physiology, biomarkers, quality of life, and composite measures of asthma control.

Symptoms. The goal of asthma therapy is to minimize symptoms, optimize lung function, and prevent exacerbations. The classic 4 symptoms are wheezing, shortness of breath, cough, and chest tightness. However, asthma symptoms are nonspecific, and their occurrence and individuals' perception of them vary among patients. Although increased symptoms and SABA use are characteristic of exacerbations, there are currently no validated criteria for the magnitude of change in symptoms that defines an asthma exacerbation. In addition, it is difficult to establish explicit definitions for "exacerbation," given the range of values reported. A wide range of symptom score scales is available in the literature, with ordinal scales ranging from 0 to 3, 10, and 12. Most studies distinguish between daytime and nighttime symptoms and night waking. However, some instruments ask a global question about "asthma symptoms" without further clarification, whereas in other studies the individual asthma symptoms of wheezing, dyspnea, chest tightness, and cough are detailed separately. A frequent metric is the symptom-free day, asthma-free day, or conversely, the asthma-symptom day, but the way the questions are asked about individual symptoms influences the ability to satisfy criteria for a symptom-free day**.** Symptom measures also vary in the way they either assess or distinguish among the frequency, intensity, or impact of symptoms on normal activities. In pediatric assessments diary completion by the parent or caregiver rather than by the child also may lead to underreporting. Further work to develop a symptom measure for inclusion in a component-based definition of asthma exacerbation is encouraged.

SABA use. The use of SABA for quick relief may reflect the frequency and intensity of symptoms and can be considered a surrogate measure for symptoms. The measure can be quantified as the number of inhalations, or puffs, per day or of SABA-free days. However, the use of SABAs also reflects the patient's symptom tolerance and his or her usual level of physical activity, which makes SABA use as an outcome measure more subjective. In addition, the routine dose of some SABAs can be 1 or 2 inhalations, and some SABA use is anticipatory, which adds variability. For children, SABA use is often controlled by the parent. However, the decision to use SABAs for acute symptoms is a common criterion for exacerbations in studies of asthma. In studies of adults, it was the most commonly reported component after systemic corticosteroids use, ED or UC visits, and hospitalizations for exacerbation, and it was included in 68% of the studies. A major problem is that the threshold criterion for distinguishing between loss of control and an asthma exacerbation has not been defined. Thresholds for SABA use as a definition for an exacerbation varied from greater than 3 to 12 puffs per day in pediatric studies and greater than 4 to 16 puffs per day in adult studies. Noteworthy are multiple, slight variations to capture a similar concept: The threshold for increased SABA use was defined in 12 different ways in the reviewed literature. Therefore more research on thresholds for increased use of SABAs as a component of an asthma exacerbation is required before this can be considered a core exacerbation outcome or can be used as 1 of the elements of a component-based definition of asthma exacerbation.

Physiology. Exacerbations are characterized by a decrease in expiratory airflow that can be documented and quantified by simple measurement of lung function (spirometry or PEF). FEV_1 is often cited as a recognized, valid, and reliable measure but one that requires regularly calibrated equipment and carefully trained technicians for accurate measurement. Its use is not feasible in the very young, but it can be used in children aged 5 years and older, adolescents, and adults. However, while FEV_1 remains an important asthma outcome measure, its use in defining exacerbations is less common.

A change in PEF has been used to define an exacerbation, with the level of required change varying from 20% to 35%. In several studies poor associations have been observed between PEF criteria for exacerbation and clinician prescription of corticosteroids. In the Formoterol and Corticosteroids Establishing Therapy International Study Group study, 73% of the exacerbations were identified clinically by the investigator rather than by a reduction in morning PEF.[54] Similarly, in the budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma STAY study, 87% of the exacerbations that met the fall in PEF criteria were commonly discovered on retrospective analysis of diary card data and did not result in a medical intervention.[131] This calls into question the clinical relevance of a change in PEF in prospectively defining an exacerbation. PEF has been shown to be less sensitive in identifying exacerbations than FEV_1. In 1 study 31 treatment failures were identified by a 20% or greater fall in FEV_1 compared with 7 for PEF (≤65% baseline, 2 of 3 consecutive measurements) or 4 with SABA use (≥8 puffs/day over baseline or 16 puffs/day in 48 hours). Similarly, using a 20% or greater fall in FEV_1 as the gold standard, investigators compared the utility of PEF, symptoms, and SABA use as a marker of treatment failure both used alone and used together.[132] None of the measures successfully discriminated patients with a fall in FEV_1 of 20% or greater from those without. Sensitivity and specificity were generally poor (<80%) at all cutoff values. Additional studies that defined treatment failures with multiple measures found that most treatment failures were characterized by reduction in FEV_1 or systemic corticosteroid use.[62,66]

Finally, because of the high proportion of retrospectively completed entries, data from paper PEF diaries should be interpreted with caution in the analysis of exacerbations.[133] Electronically recorded PEF data need to be considered in future validation studies because they may be more reliable. Identification of the level of change in PEF that can be included in a component-based definition of exacerbation may be valuable. In addition, FEV_1 is a recognized, valid, and reliable measure and remains an important asthma outcome measure, but its use in defining exacerbations is not currently recommended. However, its use in a composite measure defining exacerbations should be considered.

Biomarkers. Biomarkers are useful in assessing and studying the biology of exacerbation and can be included in prospective studies, within the limits of the technical capability of the tests, such as fractional exhaled nitric oxide (FENO), sputum eosinophils, and exhaled breath condensate analytes. However, biomarkers do not currently have a role in defining or diagnosing exacerbation. For example, clinical trials evaluating the use of FENO in predicting asthma exacerbation and adjusting therapy have reported variable results. Further evaluation is needed to define the role of FENO in guiding asthma management.

Quality of life. Asthma-related quality of life is a global measure of the impact of asthma from the patient's perspective, including the impact of exacerbations. The patient's perception of the burden of disease may be completely different from the clinician's and may vary according to the patient's circumstances

and expectations. While measuring health-related quality of life can add valuable information for improving assessment of the impact of asthma and asthma-related quality of life has been used for validation of other asthma-related outcomes, quality of life cannot be recommended as a component for defining exacerbations.

Composite measures for asthma control. The distinction between loss of asthma control and a progression to exacerbation is blurred and characterized by vague and inconsistently used terminology. The use of such measures to define an exacerbation is not recommended.

Stratification by severity

The EPR-3 guidelines note that acute exacerbations can be mild, moderate, or severe in any category of persistent asthma. The ATS/ERS statement on the standardization of outcomes defines "moderate" and "severe exacerbation" but excludes "mild exacerbation" from its recommendations. The ATS/ERS statement excludes a definition of "mild exacerbation" because it is hard to distinguish these episodes from the normal variation for the individual patient or from transient loss of asthma control. Furthermore, the ATS/ERS statement's definition of "moderate exacerbation" is limited because it does not include objective criteria to for the threshold values necessary to operationalize its use in clinical trials.

Terms such as "mild," "moderate," and "severe" represent categorical classifications that require agreement on which clinical measures are used to classify severity, as well as agreement on threshold criteria. Whether these focus on the frequency of night waking, SABA use, or lung function values, setting thresholds that allow one to distinguish between uncontrolled asthma and an exacerbation poses significant challenges. The majority of the individual parameters that can assess asthma status are continuous traits, and identification of threshold values or creation of categorical variables can be arbitrary. Furthermore, the number of days of change in status that are required to label something an exacerbation needs to be determined.

Nevertheless, the concept of a moderate exacerbation has utility because early treatment of asthma exacerbations is the best strategy for management. It is reasonable to consider a definition of asthma exacerbation that includes one of lesser severity (ie, deterioration in symptoms and/or lung function with increased SABA use but not severe enough to warrant systemic corticosteroid use and/or a hospital visit). However, further investigation is needed to define criteria to standardize the thresholds distinguishing uncontrolled asthma from a moderate exacerbation for either prospective or retrospective clinical trials. Therefore severity classification of exacerbations is an emerging outcome.

Systemic corticosteroid dosing and duration of treatment

For oral systemic corticosteroid use, a potential problem with reporting in both retrospective and prospective studies is the lack of quantification of dosage or duration of treatment. In addition, trial reports do not always make it clear whether the corticosteroid dose was standardized in the protocol or left to physician discretion. The most accurate measurement of corticosteroid use is milligrams of corticosteroid taken per patient per unit of time and the duration of therapy. The handling of closely consecutive courses also should be outlined.

It must be noted that many courses of corticosteroids are of a prespecified duration, independent of how quickly a patient improves; in such instances the total amount of corticosteroid taken may not accurately reflect the severity of the event. However, as a first step, recording the duration and total dosage given will improve understanding of these events and the ability to compare results across studies. This information will be less available for retrospective studies but should be reported when possible.

For prospective studies, the factors (clinical, psychological, and contextual) that contribute to patient and clinician decisions to use systemic corticosteroids or that prompt UC utilization need to be further investigated. The subcommittee proposes as a first step the development of a standardized format for capturing this information.

Factors precipitating exacerbations

Emerging science has emphasized the variability in the pathophysiology of asthma, which manifests as different clinical phenotypes. Similarly, asthma exacerbations are precipitated by different factors, such as viral infections or exposures to allergens and irritants. Therefore it is possible that exacerbation phenotypes may exist. It is further speculated that the response to an intervention during an exacerbation differs depending on the precipitating factor. To examine this concept of exacerbation phenotypes, the subcommittee recommends the development of a standard reporting format for capturing information related to these precipitating factors.

SPECIFIC ISSUES RELATED TO EXACERBATIONS AS AN ASTHMA OUTCOME MEASURE IN PEDIATRICS

Definition and methodology for measurement

There are differences in the way exacerbations are currently measured in different age groups. In addition to the use of systemic (or increase in inhaled) corticosteroids, other frequently used measures for diagnosing an asthma exacerbation in a pediatric population include documentation of respiratory signs and symptoms, symptom scores, use of SABAs, and response to SABAs. Objective measures, including pulse oximetry, and exhaled FENO also have been used for defining exacerbations in children and characterizing the severity of these exacerbations. Practical measures of lung function are not routinely available for children aged 0 to 4 years, and there are notable individual variations in use of lung function measures in children aged 5-11 years. The following sections discuss various definitions of asthma exacerbations in children.

Asthma exacerbations in children aged 0-4 years

Asthma exacerbations in children aged 0 to 4 years are difficult to identify for several reasons. Foremost, the differentiation of changes in daily symptoms from a potential cluster of symptoms sufficient to be termed an exacerbation is based on the perception of the caregiver and not the child. The threshold for symptom identification and initiation of therapy depends on the education level and personality of the caregiver. Objective metrics to identify exacerbations are difficult to determine and have not been used in large clinical trials. A further complication in this age group is that wheezing from causes unrelated to asthma, including viral respiratory tract infections, is common. Further

research is needed to develop reliable identification of different wheezing phenotypes and treatment responses to allow for precise definitions of exacerbations in this age group.

Current asthma guideline definitions for children aged 0-4 years. The EPR-3 asthma guidelines emphasize the importance of the physical examination and not objective measurements in the assessment of an asthma exacerbation in preschool children. Use of accessory muscles, inspiratory and expiratory wheezing, paradoxical breathing, cyanosis, and tachypnea are all cited as signs of respiratory distress. The most important objective measurement proposed is the percentage of available hemoglobin that is saturated with oxygen, which, if less than 90%, can indicate serious respiratory distress. Lack of objective improvement in the physical examination following treatment with SABAs is given as an indicator for hospitalization. Treatment with a systemic corticosteroid is recommended early in an asthma exacerbation of a preschool child or infant.

The GINA guidelines define an exacerbation of asthma in children aged 5 years and younger as an acute or subacute deterioration in symptom control that is sufficient to cause distress or risk to health, necessitating a visit to a healthcare provider or requiring treatment with systemic corticosteroids. Early symptoms of an acute exacerbation may include any of the following: an increase in wheezing and shortness of breath; an increase in coughing, especially nocturnal cough; lethargy or reduced exercise tolerance; impairment of daily activities, including feeding; and a poor response to SABA medication.

Review of definitions of "exacerbation" in clinical trials. Two large NHLBI-funded clinical trials involving wheezing exacerbations have been conducted in preschool children.[30,31] In the Preventing Early Asthma in Kids trial[30] participants aged 12 to 59 months with a positive asthma predictive index (an indicator of risk factors for developing persistent asthma) received 2 years of inhaled fluticasone or placebo to determine whether the inhaled corticosteroid had an impact on asthma-control days in year 3. Exacerbations were defined as a course of oral systemic corticosteroids to control asthma-like symptoms.

In the Acute Intervention Management Strategies study[31] early signs of episodic respiratory tract illnesses were treated with either inhaled budesonide or montelukast in children aged 12 to 59 months to prevent the development of an exacerbation. However, like the Preventing Early Asthma in Kids trial, the Acute Intervention Management Strategies study defined an exacerbation as an episode requiring the use of oral systemic corticosteroids given according to a predetermined protocol.

A phase III industry-sponsored study compared the effectiveness of budesonide inhalation suspension to montelukast over 52 weeks in children 2 to 8 years of age with asthma.[26] The mean age of study participants was 4.8 years. The primary endpoint in the trial was time to first additional medication for worsening asthma within 52 weeks. Time to first asthma exacerbation was a secondary endpoint and was defined as the time to either a doubling of inhaled corticosteroids or an oral systemic corticosteroid burst. This study also defined mild versus severe exacerbations: a mild asthma exacerbation was defined as the need for 3 or more doses of SABAs on 4 of 7 consecutive days or as having nighttime awakenings caused by asthma symptoms on 2 or more of 7 days during each of 2 consecutive weeks. A severe asthma exacerbation was defined as one needing 6 doses of SABA in a 24-hour period, 10 doses of SABA in a 48-hour period, or hospitalization for worsening of symptoms.

Summary for children aged 0-4 years. There is no well-validated objective definition of an asthma exacerbation in preschool children. Available clinical trials use the following definitions: (1) a burst of corticosteroids to control acute asthma-like symptoms, (2) complex algorithms utilizing individual symptom profiles, or (3) symptoms that persist despite treatment with a SABA. Specific thresholds for these definitions have not been well established because of the small number of subjects studied and because of variations in inclusion and exclusion criteria. The same constraints apply to the repeatability, responsiveness, validity, and associations for each of the definitions used to date.

Subcommittee definition of "exacerbation" in children aged 0-4 years. An exacerbation is a worsening of asthma requiring the use of systemic corticosteroids (or for patients on a stable maintenance dose, an increase in the use of systemic corticosteroids) to prevent a serious outcome. However, evidence in pediatric acute care supports the use of only 1 to 2 days of dexamethasone to achieve better adherence and similar outcomes.[89-91] Therefore the requirement for 3 days of systemic corticosteroids to define an event as an exacerbation for adults is not included in the definition of an exacerbation for children aged 0 to 4 years.

Outcome measures for asthma exacerbation in children aged 0-4 years. The subcommittee recommends that the core outcomes for asthma exacerbations in prospective clinical trials for children aged 0 to 4 years should be the same as for adolescents and adults (Table III):

A. all worsening asthma events in which systemic corticosteroids are initiated or increased to prevent a serious outcome (these include use of systemic corticosteroids in association with any form of healthcare provider encounter);
B. all asthma-specific ED or UC visits that involve treatment with systemic corticosteroids;
C. all asthma-specific hospitalizations that involve treatment with systemic corticosteroids;
D. all asthma-specific ICU admissions or intubations; and
E. all deaths (all cause and asthma related).

Additional features characterize asthma exacerbations of preschool children and are considered supplemental outcomes. These features include tachypnea (respiratory rate >60 breaths/minute), hypoxemia (oxygen saturation, <90% of predicted value), cough, and retractions, and are included in a number of composite assessment tools, such as the Pediatric Asthma Severity Score,[3] Asthma Severity Score,[1] Clinical Asthma Score,[2] Preschool Respiratory Assessment Measure,[5] Pulmonary Index,[4] and Pulmonary Score.[6] For this age group, these tools can be used to assess the severity of an exacerbation in ED and UC settings and as outcome measures testing the effectiveness of an intervention.

The recommendations for reporting exacerbation outcomes are outlined in Table V. Measures to characterize the study populations are important because they will enhance analysis and interpretation of clinical trial or observational study outcomes and are listed in Table III.

Asthma exacerbations in children aged 5-11 years

Children aged 5 years and older can be expected to provide information about symptoms, and the majority can perform lung

function testing and home monitoring of PEF. The principles of medical therapies to relieve acute symptoms of asthma in this age group are similar to those used to treat adults. Collectively, this means that the quality of the data that can be used in exacerbation definitions is similar to that obtained in studies of adults.

We reviewed pediatric asthma treatment studies in which asthma exacerbation was used as either a primary or secondary outcome. This review focused on identifying the prevalence of the use of different measures for defining asthma exacerbations, as well as the supporting evidence base. A total of 15 NIH-funded studies[18,20-27,30,31,33,35-37] and 5 phase III industry-sponsored studies[11,13,15-17] were identified that included children aged 5 to 11 years (with some variation in upper and lower age limits). Six additional studies included children aged 5 to 11 years together with adolescents.

Review of definitions of "exacerbation" in clinical trials. The review identified 4 main themes: (1) exacerbation was seldom used as a primary outcome; (2) definitions for exacerbation were not always clearly stated in the protocols; (3) there was considerable variability in the definitions; and (4) most of the definitions were composites of multiple measures. A subset of studies (11 NIH studies and 4 industry-sponsored studies) provided enough detail to assess specific criteria for defining exacerbation. As for adolescent and adult populations, the most common definition for children aged 5 to 11 years was the use of systemic corticosteroids, followed by hospitalization or ED visit. The frequency and duration of SABA use; a decrease in PEF; and symptoms such as wheezing, nocturnal waking, and persistence of symptoms after treatment also were reported, but there was considerable variation regarding whether and how these measures were reported within the trials.

The use of SABAs in the context of acute worsening of symptoms of asthma is a historically employed, almost universal criterion for asthma exacerbations within pediatric populations. It is also used in EPR-3 to help define exacerbations. SABA use reflects a need for more vigorous treatment and can be either a binary measure or a continuous measure. When a continuous measure, SABA use can be expressed as the number of puffs or nebulizer treatments in the course of a study period, the time to the first dose, or both. However, the subcommittee only recommends SABA use as an emerging outcome because usage patterns of SABA reflect provider, patient, or caregiver judgment with remarkable variation in the decision criteria. Better definition of these criteria is crucial in determining validity of this measure. In addition, although this measure is commonly used, the cutoff values that define an exacerbation have not been validated. For these reasons, the subcommittee recommends SABA use as an emerging outcome in this age group.

Biomarkers offer some promise for defining exacerbations, including sputum assays, FENO, and assays of exhaled breath condensate. These samples are relatively easy to collect in adolescents and can be potentially collected in children aged 5 to 11 years. However, these samples are difficult to collect in younger children. In general, they can help identify loss of asthma control, identify patients at risk for exacerbations, shed light on the biology of an exacerbation, and potentially aid the prognosis for resolution of disease. However, these measures have not yet been validated for the purpose of defining an exacerbation.

Subcommittee definition of "asthma exacerbations" in children aged 5-11 years. The definition of asthma exacerbation for children aged 5 to 11 years is the same as that for children aged 0 to 4 years. As is the case with the recommendation for young children (0-4 years), the requirement for 3 days of systemic corticosteroids to define an event as an exacerbation is not included for children aged 5 to 11 years because evidence in pediatric acute care supports the use of only 1 to 2 days of injected or oral dexamethasone to achieve better adherence and outcomes similar to the use of oral systemic corticosteroids.[89-91]

Outcome measures for asthma exacerbations in children aged 5-11 years. The core outcome measures for children aged 5 to 11 years are the same as those listed for children aged 0 to 4 years (Table III). FEV_1 is listed as a supplemental outcome for children aged 5 to 11 years, when feasible, whereas FEV_1 is not a feasible measure for the 0- to 4-year age group.

Future directions and research questions related to pediatric populations

Component-based definition of "asthma exacerbations." As with adult and adolescent populations, the subcommittee believes that a component-based definition of asthma exacerbation is also needed in studies involving populations aged 11 years and younger. It is not possible to predict at this point whether the ideal component definition for asthma exacerbations will be the same for pediatric populations as for adults or whether preschool children will require a definition different from that of older children.

Currently, there are multiple components in the various definitions for "exacerbation," but there was little evidence to support a choice of 1 or more of these components as the best definition. There is some evidence that composite definitions for exacerbations are better indicators of treatment response than a single indicator; however, existing component-based definitions have not been directly compared with one another. In addition, there is a lack of consensus regarding specific criteria and cutoff values for individual components. Establishing a component-based definition of asthma exacerbations to be used in future clinical trials is an important task for the future.

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Asthma outcomes: Quality of life

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Background: "Asthma-related quality of life" (QOL) refers to the perceived impact that asthma has on the patient's QOL.
Objective: National Institutes of Health institutes and other federal agencies convened an expert group to recommend standardized measures of the impact of asthma on QOL for use in future asthma clinical research.
Methods: We reviewed published documentation regarding the development and psychometric evaluation; clinical research use since 2000; and extent to which the content of each existing QOL instrument provides a unique, reliable, and valid assessment of the intended construct. We classified instruments as core (required in future studies), supplemental (used according to the study's aims and standardized), or emerging (requiring validation and standardization). This work was discussed at an National Institutes of Health-organized workshop convened in March 2010 and finalized in September 2011.
Results: Eleven instruments for adults and 6 for children were identified for review. None qualified as core instruments because they predominantly measured indicators of asthma control (symptoms and/or functional status); failed to provide a distinct, reliable score measuring all key dimensions of the intended construct; and/or lacked adequate psychometric data.
Conclusions: In the absence of existing instruments that meet the stated criteria, currently available instruments are classified as either supplemental or emerging. Research is strongly recommended to develop and evaluate instruments that provide a distinct, reliable measure of the patient's perception of the impact of asthma on all of the key dimensions of QOL, an important outcome that is not captured in other outcome measures. (J Allergy Clin Immunol 2012;129:S88-123.)

Key words: *Asthma burden, asthma-related well-being, health perceptions, health status, patient-reported outcomes*

Abbreviations used

ABP:	Asthma Bother Profile
AIS-6:	Asthma Impact Survey
AQ-20:	Airways Questionnaire-20
AQLQ:	Asthma Quality of Life Questionnaire
AQLQ-S:	Asthma Quality of Life Questionnaire–Standardized
ASF:	Asthma Short Form
ATS:	American Thoracic Society
BMI:	Body mass index
CHSA:	Child Health Survey for Asthma
CHSA-C:	Child Health Survey for Asthma–Child Version
COPD:	Chronic obstructive pulmonary disease
ERS:	European Respiratory Society
M-AQLQ-Marks:	Modified Asthma Quality of Life
MCID:	Minimal clinically important difference
Mini-AQLQ:	Mini-Asthma Quality of Life Questionnaire
NIH:	National Institutes of Health
PACQLQ:	Pediatric Asthma Caregiver Quality of Life Questionnaire
PAQLQ:	Pediatric Asthma Quality of Life Questionnaire
PedsQL:	Pediatric Quality of Life Inventory
PedsQL 3.0 Asthma Module:	Pediatric Quality of Life Inventory 3.0 Asthma Module
Pictorial PAQLQL:	Pictorial Quality of Life Measure for Young Children With Asthma
QOL:	Quality of life
SGRQ:	St George's Respiratory Questionnaire
WISC:	Wechsler Intelligence Scale for Children

Asthma clinical research lacks adequate outcomes standardization. As a result, our ability to examine and compare outcomes across clinical trials and clinical studies, interpret evaluations of new and available therapeutic modalities for this disease at a scale larger than a single trial, and pool data for observational studies (eg, genetics, genomics, and pharmacoeconomics) is impaired.[1] Several National Institutes of Health (NIH) institutes that support asthma research (the National Heart, Lung, and Blood Institute;

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TABLE I. Recommendations for classifying asthma-related QOL measurement instruments for NIH-initiated clinical research

	Characterization of study population for prospective clinical trials (ie, baseline information)	Prospective clinical trial efficacy/effectiveness outcomes	Observational study outcomes*
Core outcome instruments	None	None	None
Supplemental instruments	Same as for "Prospective clinical trial efficacy/effectiveness outcomes"	Adult 1. ABP 2. AIS-6 3. AQLQ-S 4. Mini-AQLQ 5. LWAQ 6. Modified AQLQ-Marks 7. SGRQ 8. AQ-20 Pediatric 1. CHSA 2. PAQLQ 3. Pediatric Caregiver AQLQ 4. PedsQL 3.0 Asthma Module	Same as for "Prospective clinical trial efficacy/effectiveness outcomes"
Emerging instruments		1. CHSA-C 2. Pictorial PAQLQ	
Call for new instruments		Develop and evaluate instruments appropriate for different age groups that provide a separate measure of the patient's perception of the impact of asthma on QOL (distinct from symptoms and functional limitations).	

See Tables III and IV for methods for measuring and reporting QOL measures.
AQLQ, Asthma Quality of Life Questionnaire; *CHSA,* Child Health Survey for Asthma; *PAQLQ,* Pediatric Asthma Quality of Life Questionnaire.
*Observational study designs include cohort, case-control, cross-sectional, retrospective reviews; genome-wide association studies; and secondary analysis of existing data. Some measures may not be available in studies using previously collected data.

National Institute of Allergy and Infectious Diseases; National Institute of Environmental Health Sciences; and the Eunice Kennedy Shriver National Institute of Child Health and Human Development), as well as the Agency for Healthcare Research and Quality, have agreed to an effort for outcomes standardization. This effort aims at (1) establishing 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) identifying promising outcome measures for asthma clinical research that require further development. In the context of this effort, 7 expert subcommittees were established to propose and define outcomes under 3 categories—core, supplemental, and emerging:

- *Core outcomes* are identified as a selective set of asthma outcomes to be considered by participating NIH institutes and other federal agencies as requirements for institute/agency-initiated funding of clinical trials and large observational studies in asthma.
- *Supplemental outcomes* are asthma outcomes for which standard definitions can or have been developed, methods for measurement can be specified, and validity has been proved but whose inclusion in funded clinical asthma research will be optional.
- *Emerging outcomes* are asthma outcomes that have the potential to (1) expand and/or improve current aspects of disease monitoring and (2) improve translation of basic and animal model–based asthma research into clinical research. Emerging outcomes may be new or may have been previously used in asthma clinical research, but they are not yet standardized and require further development and validation.

Each subcommittee used the recently published *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) as a starting point and updated, expanded, or modified its recommendations as the subcommittee deemed appropriate. Each subcommittee produced a report that was discussed, modified, and adopted by the Asthma Outcomes Workshop that took place in Bethesda, Md, on March 15 and 16, 2010. The reports were revised accordingly and finalized in September 2011. The workshop's recommendations in regard to asthma-related quality of life (QOL) are presented in this article.

Asthma-related QOL as an outcome measure refers to the perceived impact that asthma has on the patient's QOL. Historically, QOL instruments were key to measuring the burden of a disease as perceived by the patient. Many currently available asthma-related QOL instruments were developed prior to formulation of the construct of asthma control. Hence these so-called asthma-related QOL instruments often included (or totally consisted of) items that focused on quantifying the individual's functional status (ability to perform daily functions and limitations on daily or desired activities) or health status (frequency and intensity of asthma symptoms, need to use short-acting β-agonist (SABA), need for urgent medical care), and/or social or emotional functioning. Few items were included that directly assessed how and how much the patient's health or functional status affected his or her QOL. In the meantime growing emphasis has been placed on patient-reported outcomes for clinical research, and the lines between patient-reported outcomes in general and measures of perceived impact of a disease on QOL have become blurred or overlapping. Separate measures of the domains of functional status and health status, as reported by the patient, have now been developed, with greater attention to objectivity, to unique measurement challenges of each domain, and to potential data sources

TABLE II. Key points and recommendations

1. QOL is an important dimension of asthma outcomes, distinct from other outcome measures of clinical signs and symptoms.
2. Currently available QOL instruments vary in the domains they measure. By definition, asthma QOL instruments should measure patients' personal perceptions of the impact of asthma on the quality of their lives. Many current QOL instruments measure a different domain—namely, impairment, which may include the patient's symptoms or functional status (ie, the ability to perform daily activities or some set of minimum physical activities). Some instruments measure asthma's impact on social, psychological, and emotional well-being, as well as financial status. Although, in general, we would expect higher symptom levels and poorer functional status to be associated with reduced QOL, a patient's perspective on disease impact can vary greatly as a function of the patient's own priorities, expectations, and lifestyle. Thus a key defining characteristic of any measurement of QOL is that it should assess the degree to which impairment matters to the patient.
3. It is important to identify exactly what an instrument measures and what domain(s) generate the scores derived from the questionnaire.
4. Although internal consistency, reliability, and concurrent/predictive associations with other outcomes has been established for a number of instruments, many suffer from 1 or more of the following limitations:
   - Lack of information about key development or validation processes.
   - A mixture of domains within the same instrument and summary scores that are based on items from multiple domains. For example, many instruments comprise mainly symptom or functional status items, which are included in a total score, with few items assessing patients' perspectives on how they are affected by these conditions.
   - Subscores being reported and recommended despite limited evidence regarding subscore discriminant validity (ie, that each subscore provides unique information). Evidence of an acceptable level of discriminant validity is essential to justify reporting and use of instrument subscores.
   - Lack of information about core psychometric properties.
   - Either complete lack of information on an MCID or else use of questionable methodology to establish a value for MCID. This is important because achieving differences between groups or changes in the same individuals over time that meet or exceed the MCID plays a critical role in evaluating the benefit of a medical or other treatment.
   - Limited validity data on populations that are disproportionately affected by asthma (ie, low-income or minority populations) or for low-literacy populations.
5. No particular QOL instrument is recommended as a "standard." Selecting from the currently available instruments (see Tables III and IV) will depend on the domains of interest and the characteristics (eg, demographics, practicality) most relevant to a particular clinical research project.
6. Many instruments have been translated into languages other than English; several used rigorous translation and back-translation methods. Such rigor is encouraged to address the cultural context of questions.
7. QOL instruments also need to be age appropriate. Caution should be used with instruments that cover a wide age range because these may not adequately account for different age-related developmental capabilities. Furthermore, there are limited data on the use of QOL instruments for the elderly, among whom there may be confounding issues of comorbidities.
8. There is benefit in using even imperfect QOL instruments if their domain coverage includes content that taps dimensions of QOL and there is an accurate understanding of any limitations. QOL is an important construct for characterizing patient populations and evaluating therapeutic interventions, and this construct is not captured in other biological or clinical asthma outcome measures or even measures of functional status or other patient-reported outcomes. Functional status and symptoms are increasingly viewed as domains of asthma control, and measures of these constructs have been recommended in this article.
9. Research is strongly recommended to develop instruments that provide a separate measure of the patient's perception of the impact of asthma on QOL and that tap all the key dimensions of QOL. Instruments that focus on the patient's perspective on asthma's impact on his or her QOL could add unique value to the "toolbox" of asthma assessments and outcome measures.

MCID, Minimal clinically important difference.

(see "Asthma symptoms" and "Composite scores of asthma control" articles). Because the burden of disease, as measured by symptom or activity levels, does not give a complete picture, an assessment of the patient's perception of the impact of these impairments on his or her QOL remains essential. A new generation of QOL instruments is needed to focus more specifically on the patient's perception of the impact of asthma on QOL, so that there is less conceptual overlap in measures.

There is a need to question the assumption that the degree of asthma control (as manifest in symptom frequency and intensity, lung function, or impairment in physical activities) correlates perfectly with the way the patient perceives the impact of asthma on QOL. Considerable clinical experience and research evidence suggest that patient perceptions of the impact of asthma vary to an extent that is not explained by differences in asthma control or the various components of control. In fact, clinicians may gain important information when separate measures of these constructs do not covary and by trying to understand the reason for such discrepancies. If multiple domains are incorporated in future QOL instruments, the various constructs should not be mixed in a single score. The ability of an asthma QOL instrument to distinctly and reliably measure the perceived impact of asthma on QOL gives that instrument a unique value in the "toolbox" of asthma assessments and outcome measures, over and above the value provided by symptom scores or composite measures of asthma control.

Tables I and II in this article present a summary of the recommendations and key points proposed by the subcommittee. This article also includes Tables III and IV that describe the key characteristics and measurement properties of currently available instruments (9 adult instruments and 6 pediatric instruments): a narrative summary evaluation of each instrument's ability to measure the construct of the perceived impact of asthma on QOL, the instrument's practicality and demographic generalizability, and finally, a general recommendation regarding the use of each instrument.

To develop this article, each Quality of Life Subcommittee member was assigned to review several instruments and report back to the full subcommittee. The review included obtaining the published documentation of the original instrument and its development and validation studies, as well as a search of the recent literature (since 2000) regarding its use in clinical research.

See Tables III and IV for descriptive information about each instrument. Evaluative summaries also were reported to the subcommittee for review and as a basis for development of recommendations and key points regarding the measurement of asthma QOL. Furthermore, an independent literature search and review of the instruments was conducted to validate the subcommittee findings and to ensure that all relevant instruments and published asthma clinical research studies in which the instruments were used were identified. The subcommittee met through regularly scheduled telephone conference calls. Recommendations and key points required approval by all members.

This review of QOL instruments builds on the 2009 ATS/ERS statement by providing more detail on each instrument, which may assist researchers in selecting the most appropriate instrument for their studies, and by providing a more detailed assessment of the content domains of the instruments. Key objectives of the review were to consider evidence and to:

- determine what, specifically, is being measured and not measured by existing instruments intended to assess QOL;
- identify the extent to which each instrument includes items measuring patient perception of the impact of asthma on his or her QOL;
- identify conceptual confusions and critical distinctions between different types of instrument content; and
- provide information that would allow a comparison of the content and other properties, as well as what is known and not known about the various instruments.

In addition, we saw a need to carefully evaluate the psychometric properties of instrument scores (reliability, cross-sectional, or predictive associations with other measures; responsiveness to changes or differences in asthma status; subscale score uniqueness; and minimal clinically important score differences) and the way these properties were determined in relation to the established standards for psychological measurement tools as set forth by the relevant professional associations.

The ATS/ERS statement includes comments on generic health-related QOL questionnaires. The statement notes that generic instruments were generally designed for use by individuals with no functional limitations or symptoms or with only the most common ones (eg, mobility limitations and pain). The utility of these instruments is questionable in the context of asthma, and they should be complemented by use of a more specific tool. Consequently, the Quality of Life Subcommittee chose to focus entirely on reviewing asthma-related QOL instruments. Summaries of the recommendations regarding Quality of Life are summarized in Tables I and II.

ASTHMA-RELATED QOL AS AN OUTCOME MEASURE

Definition

Asthma-related QOL, as an outcome measure, refers to the perceived impact of asthma on a patient's (ie, respondent's) QOL. As noted, several constructs have historically been included in QOL measures: health status (eg, symptom levels), functional status (eg, activity capabilities or impairments), and the patient's perception of the impact of these impairments on his or her QOL. Other functional domains and symptomatology, such as emotional well-being, depression or anxiety, and social function, also have been included in some instruments, with or without specific inquiry as to whether the patient's asthma (as opposed to other factors) affects his or her status in these respects or his or her QOL. Acknowledging that there are overlaps among these domains, as well as correlations among items measuring different domains, researchers still must consider the extent to which the scores on available instruments reliably assess the unique construct of interest—the patient's perspective on the effects of asthma on QOL. These effects could potentially arise from many different sources, including symptom intensity and frequency, activity limitations and/or impairments, environmental restrictions and the need to avoid precipitants, the cost of medications and asthma medical care, disruptions in plans, limitations or disruptions of employment and career choices, and adverse effects on personal relationships.

One might expect that greater frequency and intensity of symptoms would be associated with greater impairment in physical, social, and/or emotional function—and, in turn, with more negative consequences for the patient's QOL—leading to the assumption that it would only be necessary to assess these domains to determine the impact of asthma on an individual's QOL. However, the degree to which the patient's QOL is compromised by any particular level of symptoms and/or functional limitations is a different construct, and the way this is evaluated by the patient may vary as a function of the patient's own priorities, expectations, and lifestyle and not solely as a function of objective functional status or symptoms. For example, a woman who prefers a sedentary lifestyle and has no reason to climb stairs at work or home may not be as bothered by the inability to climb a flight of stairs without becoming short of breath as would someone whose lifestyle requires that he or she be able to do this. On the other hand, this patient may have chosen a sedentary lifestyle because she could not be active without experiencing asthma symptoms (ie, she has adapted her lifestyle to accommodate her disease) and has accepted this without further thought. Given options or a need to be more active or reasons to view a sedentary lifestyle as problematic, she might view this functional limitation differently. Only by measuring both functional status and the patient's perspective on this status, and its impact on his or her well-being, can a complete picture emerge.

Historically, the term "quality of life" has generally encompassed multiple and potentially overlapping domains intended to characterize the burden of disease as perceived by the patient—in other words, a range of different types of patient-reported outcomes. As instruments have been refined and constructs and methods for monitoring asthma outcomes have evolved, more specificity is possible and desirable. In this article "functional status" and "health status" refer to degree of impairment. The impact of asthma on a respondent's QOL refers to how much that degree of impairment, as well as the asthma symptoms and the treatment of the condition, matters to the patient and adversely affects his or her QOL.

Methodology for measurement

Subcommittee members identified and evaluated the psychometric properties of the different QOL instruments. The review considered instruments' content validity, internal consistency, and other forms of reliability; concurrent and predictive validity; responsiveness; the discriminant validity of the overall instrument

score relative to other asthma assessment instruments; and, if the instrument included subscale scores, the discriminant validity of these subscores. An overview of measurement psychometric properties, based on standards issued jointly by the American Educational Research Association, American Psychological Association, and National Council on Measurement in Education,[3] is presented below as the context for the QOL subcommittee's review of QOL instruments. Particular considerations regarding the psychometric properties of QOL instruments also are discussed.

Administration of currently available paper-and-pencil asthma QOL instruments is either through patient self-administration or through interviews with patients or caregivers. An emerging method uses computer-assisted questionnaire administration, and 1 case used a computer-tailored assessment.

Content validity of a measurement instrument, regardless of whether it is measuring physical, biological, or psychological phenomena, refers to the extent to which the instrument measures what it is intended to measure, which is integral to whether the results of the measurement serve the purpose(s) for which they are intended. A prerequisite for valid use of an instrument for a particular purpose, even before consideration of the instrument's reliability or criterion validity, is its content validity. This is usually considered to have 2 aspects. *Face validity* is the apparent relevance of the content of the measure as judged by potential users, subject matter experts, or experts in the development of psychometric instruments. *Construct validity* refers to the adequacy of the empiric evidence and/or the theoretic rationale behind the choice of content in constructing the measurement instrument and also may be supported by information on the pattern of the associations and nonassociations between the instrument score and any subscale scores and other measures, either concurrently or predictively. For example, a stadiometer for determining height would have little plausible validity as an instrument to measure lung function, despite its reliability or the association between its measurements and lung function. Similarly, asthma symptom frequency and intensity may be an important patient-reported outcome and could be measured reliably, and the measurements could correlate well with other asthma outcomes. Nevertheless, a patient's report of his or her symptoms is not a direct assessment of the patient's perception of the impact asthma has on his or her QOL.

The issue of content validity is emphasized in this article because prior evaluations of instruments intended to measure asthma-related QOL have failed to address this issue adequately. In our review we noted that many published reports on the development of such instruments have failed to provide an explicit rationale for the instrument's content. Those that have done so have often adopted the view that such instruments should measure dimensions that are important to asthmatic patients in general (ie, what bothers or concerns them). What has been lacking are careful distinctions in the construction of items, between measurement of symptom frequency and intensity, measurement of functional impairments or limitations imposed by asthma, and measurement of other concerns (eg, dying as a result of asthma) versus measurement of the impact of these and other factors on the quality of the patient's life, as perceived by the patient.

Moreover, in recent years, other measures of asthma symptoms have been developed, both separately and as 1 aspect of composite measures of asthma control. The inclusion of items concerning symptoms and functional status and, in some cases, items assessing other aspects of asthma (eg, the need to avoid environmental triggers) in measures of QOL may be outdated or conceptually confused and may result in instruments that are redundant with other, more recent measures of asthma control. This has many implications for the creation of an efficient yet comprehensive "toolbox" of asthma outcome measures for research and clinical purposes. In some QOL instruments items that assess asthma symptoms constitute a substantial proportion of the instrument and may be very highly correlated with the remaining items, the majority of which measure functional status. In such cases and especially when evidence regarding the discriminant validity of the various subscales or components of the instrument is not available, it is not clear that the total score or any of its subscores provides unique information that would not otherwise be captured, perhaps more effectively, by separate measures of symptoms or functional status or even by a composite measure of asthma control. Hence the subcommittee emphasizes the need to carefully consider the content of any QOL instrument when selecting outcome measures for a research project.

Reliability refers to the consistency or reproducibility of a measurement, and adequate reliability is essential to the validity of any measurement tool. Greater reliability is achieved when a measurement tool has a lesser amount of random measurement error. To the extent that a measurement is less than perfectly reliable, this imposes an upper bound on the validity of the instrument.

Two kinds of reliability are generally considered relevant: internal consistency and test-retest reliability. *Internal consistency reliability* refers to the extent to which all of the items in a psychometric instrument measure the same construct. Since psychological constructs are often multifaceted and because no 1 item is likely to yield a perfectly reliable assessment of the construct, reliable measurement typically requires multiple items, each of which measures some aspect of the construct of interest (eg, QOL). This consistency is reflected in the correlations among responses to different items within the instrument and in the associations between individual items and total scores based on all items purporting to measure the same construct.

Internal consistency is most often described using Cronbach's α statistic, a type of correlation coefficient. The level of internal consistency reliability that is necessary for a psychometric instrument depends to some extent on the purpose of the measure and the nature of the decisions to which it will contribute. For purposes of group comparisons, an α value of 0.70 or above is typically considered acceptable; for purposes of evaluating change at the individual level, an α value of near 0.90 is requisite. An α value above 0.90 indicates that the items are very homogeneous and suggests they are measuring a single underlying construct. For some purposes, such unidimensionality is appropriate. However, if the intended construct is multidimensional, extremely high internal consistency may mean that the measure is not sampling all the key aspects of the construct or is only measuring them in a very narrow manner. As a consequence, the validity and usefulness of the measure may be compromised.

Reliability was considered by the subcommittee with particular attention to the implications of both low and very high α values at the level of subscale scores, as well as for the instrument as a whole.

Test-retest reliability refers to the consistency, repeatability, or stability of a measurement and is typically assessed over periods during which the underlying construct can be assumed to have remained stable, which tends to mean over relatively brief time periods but periods that are sufficiently long as to reduce recall and

learning effects. Test-retest reliability is usually expressed as a correlation between 2 measurements made on the same instrument at different time points. There is no universally agreed-upon threshold for acceptable test-retest reliability. Under ideal conditions (ie, no carryover of the previous measurement, which would inflate the apparent test-retest reliability, and no underlying change in the patient's status, which would deflate the apparent reliability), a perfectly reliable instrument would result in a perfect correlation between the 2 consecutive measurements on the same patient. However, psychometric instruments are not perfectly reliable, and the preconditions of no measurement reactivity and patient stability typically do not exist. Hence test-retest reliability values of 0.70 and above, under appropriate conditions, are typically considered minimally acceptable.

Criterion validity has been the focus of most developmental studies of QOL tools to date. However, much of the literature concerning QOL measures has assumed that the higher the correlation between a QOL measure and other asthma outcome measures (eg, FEV_1, asthma symptoms, and functional status), the more valid the QOL measure. Similarly, an imperfect association has been assumed to demonstrate that the QOL measure is providing unique information. Both assumptions are open to question on a number of grounds. A very high correlation would call into question the need for the QOL measure—that is, whether it yields any unique information not provided by the other measures and whether it is a measure of QOL at all or simply a duplication of what is being measured by the outcome with which it is correlated (eg, symptoms, functional status, and healthcare utilization). A modest correlation may reflect the imperfect reliability of 1 or both measures being correlated and is not necessarily evidence that the QOL instrument provides unique information. More fundamentally, from a clinical and research standpoint, the important question with regard to QOL measures concerns the extent to which the patients' asthma (whether referring to lung function, symptom status, asthma control, costs of medications and care, need to avoid asthma triggers, or other features of their asthma) is detracting from their QOL and whether various medical or other interventions lessen this burden. In that sense the magnitude of the correlation between a QOL measure and some measure of health status or functional status is not direct evidence either for or against the validity of the QOL instrument. The correlations may reflect the extent to which patients' QOL is, on average across patients, determined by what is being measured by the variables with which the QOL instrument is being correlated versus the extent to which it is determined by the values, lifestyle, and other characteristics of the individual patient. The individual's perspective on the impact of his or her asthma rather than the individual's status on dimensions that are important or bothersome to the typical person with asthma is what QOL instruments could uniquely provide. Thus a QOL instrument's validity is best judged in terms of (1) its content (ie, whether the items require the respondent to indicate the extent to which his or her QOL is being compromised by asthma on all the dimensions on which individuals evaluate their QOL or at least on all those dimensions that might possibly be affected by asthma), and (2) whether the assessment it provides is reliable.

Responsiveness refers to the ability of a measure to detect changes in the underlying construct over a time period in which change is expected to have occurred or in which some relevant intervention was delivered and the measure's ability to detect individual differences in asthma-related QOL, such as between individuals with comparable asthma status but who have very different life circumstances, goals, or values. In QOL research responsiveness is most frequently evaluated by examining change in scores on the measure in response to asthma treatment or changes in other measures of health status (eg, lung function). Evidence that scores on a QOL measure differ in relation to disease activity or among groups with known differences in asthma severity, for example, has been considered to provide evidence of the measure's responsiveness. The converse is not the case, however. The failure of a QOL measure to detect group differences or to detect within-group changes over time is not, *per se,* evidence that the measure is unresponsive. It simply may be that the expected differences or changes did not occur, were too limited to have an impact on the patient's QOL in the context of other factors that might influence his or her QOL, or were offset by negative QOL effects of side effects of the treatment.

Medical and scientific value

It is increasingly recognized that the evaluation of therapeutic interventions should include assessment of outcomes that matter to patients. Measures of patient perspective on the impact of asthma are not fully reflected in measures of clinical signs and symptoms, lung function, or the underlying pathology on which most clinical trials focus. QOL measures can provide unique information as a component of the toolbox of asthma outcome measurements and can thus provide a more complete characterization of the study population's asthma and of the benefits or drawbacks of particular interventions.

Priority for NIH-initiated clinical research

The subcommittee considers measures of functional status to be essential for characterizing patient populations because this information is critical for understanding the type of patients included in the study. Currently available QOL instruments may be helpful in this regard, but other instruments may capture this domain more efficiently. The subcommittee recommends that QOL measures be classified as a supplementary outcome measure in prospective clinical trials and observational studies for 2 reasons. First, currently available instruments do not meet the subcommittee's expectations for performance in distinctly and robustly capturing the construct of the patient's perspective on the impact of asthma on his or her QOL. Second, the desirability of measuring this construct is highly likely to depend on the aims of a particular research project. However, the subcommittee strongly encourages researchers to consider including measures of asthma-related QOL as an outcome because, even if imperfectly measured, many currently available asthma QOL instruments can capture unique characteristics of study populations and the benefits or harms of asthma interventions that may not be otherwise assessed.

Future directions for asthma-related QOL as an outcome

If a methodological goal for asthma clinical research is to construct a toolkit of outcome measures, it would be most efficient to have each outcome measurement make a unique contribution to the whole and not duplicate what other measures accomplish. The patient's perception of asthma's impact on his or

her QOL is a unique construct and must be measured separately from other domains, such as functional status or clinical signs and symptoms. The recent development of instruments to measure functional status and health status through a composite asthma control score offers the opportunity to encourage future generations of QOL measures to focus more specifically on the patient's perception of the impact of asthma. This would avoid overlap with other measures and make a unique contribution to the ideal toolbox of asthma outcome measures.

REVIEW OF ASTHMA-RELATED QOL INSTRUMENTS

Descriptive summaries of 9 asthma-related QOL instruments for adult study populations and 4 instruments for pediatric study populations follow. The subcommittee does not recommend any instrument as a core instrument because findings from the subcommittee's review of asthma QOL instruments revealed the following limitations: most instruments include measures of functional and health status or consist entirely of these measures; none of the instruments measures the full range of dimensions that affect QOL; and few of the instruments provide a distinct score that yields a robust and individually reliable measure of the patients' perspective on their QOL as affected by their asthma. Thus the available instruments are listed as "supplementary."

The subcommittee has not prioritized the list for research use. At this point in time, the extent to which the content of existing instruments was uniquely directed at measurement of asthma's impact on a patient's QOL was not found to be positively associated with the extent of the instrument's prior use or the availability of data on its psychometric properties. It would be inappropriate to promote widespread use of an inadequate measure simply because of its history of use and equally inappropriate to promote the use of a promising measure that lacks adequate psychometric data. Because there are no existing instruments that uniquely measure the impact of asthma on patient QOL and have adequate psychometric data, the subcommittee elected to provide descriptions in the tables and following narrative summary, pointing out the strengths and weaknesses of the available instruments. These are provided in the hope of guiding investigators to the most appropriate instrument or instruments for the requirements of their research aims and study populations.

Each summary highlights the subcommittee's evaluation of the key features of the content domains measured by that instrument and its key strengths and weaknesses and concludes with a recommendation regarding the use of the instrument in clinical research. Tables III and IV provide detailed information for adult and pediatric QOL instruments, respectively, about the content domains assessed by each instrument; its target populations, demographic considerations, and methodological considerations (range of values, repeatability, responsiveness, validity, practicality, or risk); information about how widely the instrument has been used in published clinical studies and other research; and key references.

ASTHMA-RELATED QOL INSTRUMENTS FOR ADULT STUDY POPULATIONS

Asthma Bother Profile (developed by M. E. Hyland)

Summary. The Asthma Bother Profile (ABP) is a 22-item instrument requiring 10 minutes to complete that was developed for the primary purpose of clinical management of patients and not necessarily for use as an outcome measure in clinical studies. The ABP is designed to assess adult patients' perception of the asthma experience and distress in different situations and areas of life, as well as patients' perception of their asthma management. This asthma QOL instrument is unique among currently available instruments in its emphasis on the psychosocial impact of asthma, including items measuring perceived bother, mood, fear, social relations, and financial impact. The initial ABP questionnaire was constructed on the basis of earlier asthma QOL research and modified by patients' discussion in focus groups of the way their lives were affected by asthma. The instrument includes a 15-item scale measuring asthma bother. All 15 items measure the impact of asthma on the respondent. For example, item 4 of this scale asks, "Overall, how much does your asthma bother your personal life (such as love life, personal relationships, family life)?" No items in this bother scale measure health status or symptoms, and so the ABP comes somewhat closer than other instruments to measuring the construct of QOL as defined by the subcommittee. However, there is arguably a significant difference between asking how much an individual is "bothered" and asking about the extent and direction of the effect of asthma on the person's QOL. The instrument's 15 items are scored on a 6-point scale; at 1 end of the scale is "no bother at all" for 10 items or "I never have a worry" for 5 items; all 15 items then share the remaining scale ranging from "minor irritation," "slight bother," "moderate bother," "a lot of bother," to "makes my life a misery." The overall bother scale score is the sum of the 15 item scores. The ABP also includes a single item asking which months of the year the person is bothered by his or her asthma and a 7-item asthma management scale, which is scored separately. This 7-item scale is not intended to measure asthma QOL but instead measures psychological mediators of asthma self-management, including beliefs about self-efficacy and confidence.

Strengths and weaknesses. Strengths of the ABP include high internal consistency of the 15-item bother scale, substantial correlation of the 15-item bother scale with other QOL instruments, and good test-retest reliability. The 15 bother items exclusively focus on the perceived impact of asthma on the patient's psychological state. The total score is not directly influenced by items assessing symptom frequency or severity or functional ability. Thus this instrument is highly specific for measuring the patient's perspective on how much he or she is bothered by asthma and its impact on his or her life. Weaknesses of the instrument include very limited data on its use in clinical or research settings and lack of validated translations. The only translations studied are in Norwegian and Japanese.[4,5] No information is provided on the minimal clinically important difference (MCID) on this instrument. Only 4 published studies have cited it. The 7-item self-management scale has a weak association with the asthma bother scale, and it is unclear how its inclusion adds to the overall measure. The instrument has been shown to be sensitive to asthma self-management education; however, no published clinical trials have used this QOL measure as an outcome.

Recommendation. The subcommittee recommends classifying the ABP as a supplemental instrument for clinical research. Although the ABP has had limited utilization and was developed for clinical use, the instrument's unique focus on the psychosocial impact of asthma and mediators of asthma self-management makes it potentially useful as a supplemental outcome measure in interventional studies (including behavioral) that might alter the psychosocial impact of asthma.

Asthma Impact Survey (developed by Kaiser Permanente Care Management Institute and Quality Metrics)

Summary. The Asthma Impact Survey (AIS-6) is a brief (3-minute) 6-item asthma-specific QOL instrument intended for use by clinicians to measure the impact asthma has on their patients' lives. The AIS-6 was originally developed from a bank of 52 questions that assessed the impact of disease on physical functioning, social and role participation, emotional distress or well-being, and energy or fatigue. The authors' hypothesis for the development of the asthma impact item bank was that "the 52 items would assess one single dimension of asthma impact and that assessment of asthma impact could be based on a single score." These authors used data from a general population survey of persons with asthma and calibrated and scaled the respondents' answers using the generalized partial credit item response theory model. The authors also used the item discrimination and category parameters drawn from the generalized partial credit item response theory model to estimate information functions for each item. From this procedure, 6 items were selected that spanned a wide range of asthma impact and represented the main content areas defined by all items in the item bank (physical functioning, social and role participation, emotional distress or well-being, and energy or fatigue). The development of the AIS-6 was guided by a conceptual model that makes important distinctions between domains of health and their operational definitions. This 6-item instrument measures how much and how often asthma limits participation in normal daily activities, and also measures feelings of frustration because of asthma, specifically the social, functional, and emotional impact of asthma and its symptoms. An example of the items is the following: "In the past 4 weeks, how much did your asthma limit your usual activities or enjoyment of everyday life?" The 5 response categories range from "not at all" to "extremely." Two items of this 6-item scale assess how often in the past 4 weeks asthma has left the participant frustrated or tired. Three items assess the functional impact of asthma by asking how often in the past 4 weeks asthma has limited activities, socialization, or work. No items directly assess symptoms.

Strengths and weaknesses. Strengths of the AIS-6 include its rigorous methodological development, high internal consistency reliability, modest to substantial correlations with other asthma outcome measures, and brevity and ease of use clinically. Limitations include the relative lack of use of this instrument in clinical research, the fact that it assesses only a limited range of ways in which asthma can affect a patient's QOL, and the fee due to Quality Metrics to use the instrument. Only a total score is calculated on this short instrument.

Recommendation. The subcommittee recommends classifying the AIS-6 as a supplemental instrument for clinical research in which the brevity of the instrument is a primary consideration, but the usefulness of the instrument is limited by cost considerations and the sparse evidence of its utility for measurement of change and group differences.

Asthma Quality of Life Questionnaire–Standardized (developed by E. F. Juniper)

Summary. The Asthma Quality of Life Questionnaire–Standardized (AQLQ-S) is a 32-item instrument that targets adults and requires approximately 4 to 15 minutes to administer. It has been translated into more than 20 languages and used in international settings with ethnically diverse populations and among low socioeconomic status and ethnic minority adults with asthma in the United States. However, the psychometric properties of the instrument in various populations have not been reported, especially in low-education populations that may have difficulty understanding the items or instructions.

The AQLQ-S was based on the Asthma Quality of Life Questionnaire (AQLQ) developed previously by the same author, E. F. Juniper. The AQLQ-S differs from the original AQLQ in that it provides standardized activities that may be limited by asthma, rather than having patients generate activities, to reduce time burden and increase consistently. Other than that, its content is identical to that of the original AQLQ, and the items in both instruments concern topics derived from Kinsman's study[6] of asthmatic patients and their concerns, general health-related QOL measures, discussions with physicians, and interviews with patients. The topics include circumstances such as chest tightness, inability to carry out physical activities, experiencing symptoms resulting from cigarette smoke exposure, fear of not having medication available, and failure to get a good night's sleep due to asthma. From among a large initial set of statements, a sample of asthmatic patients identified those circumstances or occurrences that had been troublesome to them in the previous year and how important each was to them. The 32 items selected for the AQLQ-S were those that had the highest product of the proportion of individuals for whom the item was troublesome multiplied by its average importance across individuals. These items were grouped, on logical grounds, into 4 subscore domains: symptoms (12 items), activity limitations (11 items), emotional function (5 items), and exposure to environmental stimuli (4 items). No factor/cluster analysis procedure was used to ensure that the score domains were reasonably statistically independent. The composition of the initial pool of candidate items was not reported, nor was it reported whether the process of item selection eliminated items that might have tapped the impact of asthma on a wider range of dimensions of QOL (eg, social relations, financial well-being, and employment opportunities) that might be important to significant subsets of patients. The final selection, however, resulted in total scores on the AQLQ and AQLQ-S that were primarily a composite of 2 dimensions now considered to be indicators of asthma control, symptom frequency and activity limitations, plus a limited number of items that reflected the degree of negative emotions associated with asthma (concern or frustration about asthma and asthma medications and fear of shortness of breath) and how frequently the respondent encountered or had to avoid agents in the physical environment that triggered symptoms. The number of items devoted to each domain was not planned to achieve adequate reliability in the resultant subscores but simply reflected the distribution of items that survived the selection process; hence the resultant reliability of the smaller subscales is low. No evidence of an analysis of discriminant validity of the subscale scores has been found, and so it is not known how much unique information they provide; such information would be essential to justifying their reporting and use.

The items in the AQLQ and AQLQ-S are in the form of questions: "How often did you experience [or did you feel, or were you bothered/limited by] X?" "How much Y did you feel?" or "How much were you limited in doing Z?" Four different 7-point Likert-type response scales are used: a frequency scale (23 items), an amount of discomfort/distress scale (2 items), and 2

different scales assessing degree of impairment (6 items and 1 item, respectively). Each of the scale points on each Likert scale is anchored by a word or phrase, rather than being anchored only on the extremes and midpoint, which is a common and well-justified practice. The use of so many descriptors is problematic. The 4 sets of scale descriptors are: (1) "totally," "extremely," "very," "moderate," "some," "a little," and "not at all limited"; (2) "severely," "very," "moderately," "slightly," "very slightly," "hardly at all," and "not limited at all"; (3) "a very great deal," "great deal," "good deal," "moderate amount," "some," "very little," and "no discomfort"; and (4) "all," "most," "a good bit," "some," "little," "hardly any," and "none of the time." Some of these scales may be confusing to respondents because they mix adjectives with other grammatical elements, and some descriptive terms are relatively uncommon in American usage ("a good bit" and "a good deal") and rarely used in psychometric scales. There is no published evidence that the anchor words or phrases can be consistently ordered by respondents independent of their numeric positioning on the response scales or that the relative positions of different phrases represent approximately equal psychometric intervals. It is also unclear that 4 different sets of responses are actually necessary.

The statistical and psychometric methodology used to obtain an estimate of the MCID on the AQLQ/AQLQ-S and other instruments has been seriously criticized.[7-9] Without recognition of the methodological problems, the estimated MCID of 0.5 units on the AQLQ-S score scale has been widely adopted as a criterion for a clinically meaningful group mean difference and, more recently, as a criterion for the minimum clinically meaningful change at the individual level, resulting in group comparisons in terms of the proportions achieving a difference of this magnitude or greater. The AQLQ-S has been administered along with other measures of clinical improvement in many studies with repeated measures, which would permit use of the commonly recommended approach to determination of the MCID. However, the MCID for the AQLQ-S has not been re-examined in light of data from these studies, and it remains unclear whether the commonly accepted value of 0.5 units is the minimal difference that has clinical importance.

Strengths and weaknesses. Strengths of the AQLQ-S include the reliability of its total score, its responsiveness, and its widespread use and availability in many languages. It is free for use in some noncommercial clinical practice settings, but some research and strict copyright restrictions apply. The AQLQ-S provides separate and reliable measures of asthma symptoms and of asthma-related functional status (measured as activity limitations in this instrument), which are currently viewed as elements of asthma control, a construct for which other instruments have become available since the AQLQ and AQLQ-S were originally developed. Weaknesses include its substantial overlap with domains assessed by newer measures of asthma control, the overrepresentation of these items in the total score, and hence the inability to distinctly measure the patient's perspective of the impact of asthma on his or her QOL, the lack of evidence of discriminant validity of its subscales and poor reliability of the smaller subscales, and the lack of research to validate (or modify) the conventionally accepted MCID value as a criterion for assessing improvement at either the individual or group level.

Recommendation. The subcommittee recommends classifying the AQLQ-S as a supplementary instrument for situations and purposes that can be justified in light of the limitations noted above.

Mini-Asthma Quality of Life Questionnaire (developed by E. F. Juniper)

Summary. The Mini-Asthma Quality of Life Questionnaire (Mini-AQLQ) is a 15-item, asthma-specific instrument requiring 3 to 4 minutes to complete that measures health-related QOL in adults. It yields an overall score, as well as 4 subscale scores (symptoms, activities, emotions, and environment). All 15 questions are scored on four 7-point Likert scales, and the overall score and subscale scores are simple averages of the responses to their component questions. The 5-item symptom scale is a measure of symptom frequency, and the 4-item activity scale is a measure of the extent to which an individual's asthma limits his or her ability to engage in various types of activities. The 3-item emotional scale reflects the extent to which the individual's asthma triggers feelings of frustration, fear, or concern, and finally, the 3-item environmental scale reflects the extent to which individuals are bothered by or have to avoid certain airborne environmental stimuli (dust, cigarette smoke, and air pollution). The Mini-AQLQ was developed as an alternative to the original AQLQ and AQLQ-S to meet the needs of large clinical trials and long-term monitoring, where efficiency (ie, 15 items compared with 32 on the AQLQ-S) may take precedence over precision of measurement. A composite approach was used to arrive at the Mini-AQLQ from the original instruments, with the goal of including the physical and emotional impairments that adults with asthma consider most important while maintaining as much as possible the measurement properties of the original AQLQ and each of its 4 domains. First, items with high item-item correlations were evaluated by a clinician panel to see whether they were similar enough in concept to combine. Second, items in the activity domain were standardized using 4 of the 5 generic activities from the AQLQ-S. Finally, those items from the original AQLQ having the lowest impact scores in the original developmental work were removed until the prespecified number of items desired in each domain was reached. The Mini-AQLQ takes 3 to 4 minutes to administer and is free for use in some noncommercial clinical practice and research settings, with copyright restrictions as described for the AQLQ-S. The questionnaire may be self-administered or interviewer administered, although no approved online version exists. It has good reliability and responsiveness and is correlated with other measures of asthma status, but its psychometric properties are not as strong as those of the AQLQ and AQLQ-S. The Mini-AQLQ total score is still predominantly influenced by the symptom and activity domains, which collectively account for 9 of the 15 questions, although this is less an issue here than it is with the AQLQ and AQLQ-S. The Mini-AQLQ has been widely used in diverse samples, including in 21 countries outside the United States, but its psychometric properties have not been determined or reported in these latter samples.

Strengths and weaknesses. The main advantages of the Mini-AQLQ over the larger AQLQ-S are its shorter length and its more balanced representation of the subscales in the overall score. Its weaknesses are similar to those of the parent instrument, and it has lower reliability than the parent instrument.

Recommendation. The subcommittee recommends classifying the Mini-AQLQ as a supplementary instrument for use in asthma research in which efficiency is prioritized over precision of measurement.

Living With Asthma Questionnaire (developed by M. E. Hyland, et al)

Summary. The Living With Asthma Questionnaire (LWAQ) is a 68-item self-reported, self- or interviewer-administered, multidomain scale designed to measure asthma-specific QOL in adults; it takes 15 to 20 minutes to complete. The instrument was developed to provide an outcome measure for use in clinical trials, as well as to assist individual patient management. The original item set was generated through focus groups consisting of adults who had asthma, who were asked about everyday experiences of living with asthma. These were refined through standard psychometric techniques (eg, a principal components factor analysis) using data gathered from a total of 783 patients recruited from multiple clinical sites. The scale consists of 25 positively worded items and 43 negatively worded items. Responses are on a 3-point scale ("untrue of me," "slightly true of me," and "very true of me") or "not applicable." The LWAQ covers 11 domains of asthma experience: social or leisure, sport, holidays, sleep, work and other activities, colds, mobility, effect on others, medication usage, sex, and dysphoric states and attitudes. Scale scores are calculated as average scores on all applicable items after reversing the value of each negative item. In addition to providing subscores for each of the 11 domains, the LWAQ also can be divided into 2 construct subscales encompassing the patient's perception of functional limitations (also termed the "problems construct"—49 items) and the patient's perception of the emotional impact of limitations related to asthma (also termed the "evaluation construct"—19 items).

Strengths and weaknesses. While the LWAQ includes questions related to asthma symptoms and functional status, it also contains a substantial number of items (>50% of the total number) focused more specifically on the emotional and social impact of having asthma. The LWAQ is unique in that it can be analyzed in 3 different ways in a clinical trial: on the basis of an overall score, in terms of 11 domains, and from the perspective of 2 construct subscales. There is some evidence that the construct subscales differentially predict outcomes in clinical trials and are differentially sensitive to change (eg, the problems construct may be more sensitive to change over time compared with the evaluation construct; lung function and change in lung function may be more sensitive to cognitive factors than to emotional ones). There is little evidence that the individual domains differentially predict outcomes. The LWAQ has excellent internal consistency for the total scale and constructs due in part to the large number of items in this instrument. Reliability is more variable across the domain scores. This questionnaire also has good test-retest reliability and good concurrent validity. Translations of the LWAQ exist in Danish, Dutch, Finnish, French, German, Italian, Japanese, Norwegian, and Swedish, although a description of the linguistic validation process used for these translations is not readily available.

Weaknesses include the following. At 68 items, this is the longest of the asthma-specific QOL measures, which reduces its feasibility for widespread use. While the LWAQ captures a number of domains, there are some potentially important domains missing (eg, financial problems associated with asthma). Also, there is little evidence of discriminant validity for the individual domain scores or that they differentially predict outcomes, and discriminant validity is unlikely to meet conventional criteria because a single factor appears to characterize the instrument as a whole. Evidence for responsiveness of the instrument is lacking in US samples. The instrument has been used in only 1 study of lower-income subjects in the United Kingdom and has not been used in ethnically and/or socioeconomically diverse US populations.

Recommendation. The subcommittee recommends classifying the LWAQ as a supplemental instrument for clinical trials in which (1) an instrument of this length is feasible, (2) its content is appropriate for the purpose of the trial, and (3) there is a recognition of the potential overlap with more recently developed measures of asthma control that include assessment of symptoms and functional status. The LWAQ provides a reliable measure of functional limitations due to asthma and of the patient's perception of the emotional impact of those limitations.

Modified Asthma Quality of Life–Marks (developed by G. B. Marks)

Summary. The Modified Asthma Quality of Life–Marks (M-AQLQ-Marks) is an asthma-specific, self- or interviewer-administered 22-item instrument requiring less than 5 minutes to complete and designed to measure perceived QOL associated with asthma in adults. The recall period is 4 weeks. It differs from the original AQLQ-Marks in that 2 items were split into separate items and a 7-point Likert-type scale was used instead of a 5-point Likert scale. The increase in response options was designed to increase this instrument's reliability and responsiveness to change. It assesses 4 domains: (1) breathlessness (physical restrictions), (2) mood disturbance, (3) social dysfunction, and (4) concern for health. Like the original Marks instrument, it yields a total score and 4 subscale scores. Ten items appear to measure QOL, 7 measure physical symptoms and health status, and 5 measure emotional states. Unlike the original AQLQ-Marks, items on the M-AQLQ-Marks are not transformed, so that higher scores on the M-AQLQ-Marks indicate less impairment. Both the original and M-AQLQ-Marks can be administered by telephone. Both instruments attempt to ascertain how asthma affects a patient's life with regard to his or her social situation, psychological well-being, expectations, values, and perceived impact of having to avoid places or activities that could trigger increased asthma symptoms. The final items included in the original AQLQ and M-AQLQ-Marks were empirically determined. Initial identification of items for the questionnaire was derived from patients with asthma who participated in a focus group, from interviews with asthma nurse educators, and from the clinical experience of the investigators. Subsequent drafts of the instrument were subjected to validation studies with asthmatic patients. A factor analysis performed on the initial item pool confirmed that the components were broadly similar to those domains that formed the initial framework and that analysis also identified a smaller set of items that best measured 4 key domains, which now constitute subscales and make up a total score. The instrument's concurrent validity is supported by the finding that the total score and all 4 subscale scores were significantly correlated with symptoms, medication use, FEV_1, global health rating, and all SF-36 Health Survey subscales. The total score also was associated with clinical asthma severity according to the severity criteria in the National Asthma Education and Prevention Program guidelines.

Strengths and weaknesses. The M-AQLQ-Marks was developed to measure the impact of asthma on QOL. Ten of 22 questions within the 4 domains appear to assess the perceived impact of asthma on QOL, and 5 questions relate to emotional states; these 15 questions specifically deal with topics that are relevant to concerns of asthmatic patients. The M-AQLQ-Marks is user friendly and can be completed in about 5 minutes. Internal consistency and test-retest reliability are higher for the M-AQLQ-Marks than for the original instrument, although the very high internal consistency of the total score raises questions about the discriminative validity of the subscales. The instrument is responsive in that it is able to detect within-subject changes in total score over time and is associated with changes in total score and changes in symptoms, FEV_1, self-rated severity, and medication use. The minimal floor and ceiling effects of M-AQLQ-Marks demonstrate its potential usefulness as a clinical assessment tool. The M-AQLQ-Marks has been validated in a socioeconomically diverse Australian sample. Weaknesses include the consideration that its MCID of 0.5 was calculated using the same methodology used in Juniper's AQLQ for determining the MCID, which has been questioned, and only limited data exist regarding the MCID for either the original AQLQ-Marks or the modified instrument. Few clinical studies have used the M-AQLQ-Marks. Furthermore, neither the original AQLQ-Marks or the M-AQLQ-Marks has been validated in US study populations or used extensively in populations outside Australia.

Recommendation. The subcommittee recommends classifying the M-AQLQ-Marks instrument as a supplementary instrument for clinical trials in which a short questionnaire is desired; 10 of the 22 items measure patients' perception of the impact of asthma on QOL, although data on its use in clinical trials are limited.

Asthma Short Form (developed by Integrated Therapeutics Group and QualityMetrics, Inc)

Summary. The Asthma Short Form (ASF) is a 15-item, self-administered instrument requiring an estimated 3 to 4 minutes to complete. It is based on the original 20-item AQLQ-Marks instrument and items from the Integrated Therapeutics Group physical and psychosocial symptom/side effects batteries. Its purpose is to assess symptoms, functional status, and other constructs considered relevant to QOL in adolescents (aged ≥14 years) and adults. Like the AQLQ-Marks, it has a 4-week recall period and a reading grade level of 4.8 but requires only 3 to 4 minutes to administer. The ASF was created to improve on lengthy instruments (ie, LWAQ and St George's Respiratory Questionnaire [SQRQ]) and the original, nonstandardized AQLQ developed by Juniper and to eliminate item overlap between 2 subscales in the AQLQ-Marks, while retaining or improving its reliability and validity relative to that instrument.

The ASF has 5 domains: the symptom-free index (5 items), functioning with asthma (5 items), psychosocial impact (3 items), confidence in one's health/well-being (1 item), and energy (1 item). The psychometric methodology used to develop this instrument was very thorough, involving administration of items or draft forms to 3 patient samples from a clinical trial, an observational study, and a study that provided only cross-sectional data. The initial pool of 26 items was subjected to similar analyses in all 3 samples: (1) factor analysis to assign items to scales; (2) elimination of items with floor or ceiling problems and deletion of items so as to retain those that best predicted patient ratings of asthma severity, National Heart, Lung, and Blood Institute severity classification, and lost work days; (3) evaluation of the predictive ability of the shorter relative to the longer version; and (4) specification and evaluation of the short-form scale scores. Means and SDs have been reported for the ASF total and all 5 subscale scores in each of the 3 samples. Only 1 sample had any substantial representation of racial/ethnic minorities (black or Hispanic) or persons with limited education.

Strengths and weaknesses. Strengths of the ASF include its careful psychometric development, acceptable reliability, and superiority to the (longer) AQLQ-Marks in sensitivity to group differences and associations with other important asthma outcomes. Weaknesses include its relatively limited use, uncertain availability, the substantial role played by its symptom-free index in its predictive power, and the modest improvement it provides over the predictive power of a generic health QOL instrument, the physical summary and role-physical scores of the SF-36. This instrument provides separate reliable measures of (freedom from) asthma symptoms and of asthma-related functional status, but the remaining 5 items, comprising 3 scales, 2 with a single item each, do not provide a reliable measure of patients' perception of their asthma's impact on their lives.

Recommendation. The use of the ASF, even as a supplementary instrument, cannot be recommended due to its uncertain availability and its very limited assessment of patients' perceptions of the impact of asthma on their QOL.

St George's Respiratory Questionnaire (developed by P. W. Jones)

Summary. The SGRQ was designed to measure health impairment and perceived well-being (QOL) associated with airways disease, although not specifically asthma, and was seen as a potentially more responsive alternative to generic instruments, such as the Sickness Impact Profile and Quality of Well-Being Scale. The SGRQ yields a total score based on all 50 items and scores for 3 subscales (symptoms, activity, and impact) whose structure was supported by the results of a principal components analysis. The 8 questions that make up the symptoms subscale encompass the frequency, intensity, and duration of breathing symptoms. The 16-item activity subscale consists of 7 yes/no questions that reflect whether certain activities (eg, getting dressed or washed, walking outside on level ground) make the respondent feel breathless and 9 yes/no questions about whether certain activities are affected by the respondent's breathing (eg, "I take a long time to get dressed or washed," "I walk slower than other people," or "I stop for rests"). Finally, the 26-item impact subscale assesses the impact of the respondent's breathing problems on a wide variety of domains: 2 items on how great a problem the person's chest condition is; 2 items on breathlessness when talking or bending over; 4 items on sleep disturbance, tiredness, and pain associated with the person's condition; 8 items on emotions, nuisance, or uncontrollability associated with breathing problems; 4 items on how much medication affects QOL; and 6 items on whether the individual cannot engage in certain activities due to breathing problems. The majority (≥19) of the items in the impact subscale appear to directly measure the perceived impact of the respondent's breathing on QOL. These items do not assess economic impacts, however.

Altogether, the 50 items that constitute the SGRQ reflect a mix of yes/no questions and ordinal response option questions. The responses to these questions are individually weighted, with a total of 76 non–zero-weighted response options. The weights reflect the relative level of distress associated with each response and were computed by having 124 asthmatic patients drawn from 4 countries rate the degree of distress they would experience for the situation described by each individual response for each item. Ratings were made on a 10 cm visual analog scale ranging from "no distress" to "maximum imaginable distress," and the final weights were calculated by expressing the mean ratings as a percentage of the maximum possible rating of 10 cm. The weights are reported to be relatively unaffected by age, sex, and nationality and not to differ between patients with asthma and patients with chronic obstructive pulmonary disease (COPD). Due to the nature of these weights, even questions that do not directly assess the impact of the individual's asthma on QOL, such as those in the symptom subscale, may indirectly serve as a measure of the distress that is caused by these symptoms and, in that sense, may constitute a measure of the impact of asthma on the patient's QOL.

Strengths and weaknesses. Strengths include the fact that the SGRQ is free for use in noncommercial clinical practice and research. Although the SGRQ is designed for self-administration, someone should be available to answer questions, if required. Telephone administration of the SGRQ also has been validated, as has computer-based presentation, but postal administration has not. Furthermore, the scoring of the instrument is complex and should be done using a computer. The SGRQ is reliable and responsive to changes in COPD status, although less information is available on its performance in samples of individuals with asthma. The SGRQ is available in numerous languages, and evaluations of the psychometric properties of many of the translated versions have been published. Its weaknesses are the length and time to completion: at 50 items and taking 8 to 15 minutes to complete, it is 1 of the longest QOL instruments for patients with asthma. In addition, because of the way in which the response weights were constructed, the SGRQ may tap patients' perceptions of the direction and degree of impact that breathing problems have on certain dimensions of their lives, although only indirectly, but does not assess certain dimensions (eg, financial status and employment). Finally, despite its worldwide use, the psychometric properties of the SGRQ have not been assessed in a diverse sample of people who have asthma in the United States.

Recommendation. The subcommittee recommends classifying the SGRQ as a supplementary instrument for use in asthma research because of the limitations imposed by the length of the instrument.

Airways Questionnaire-20 (developed by E. A. Barley, F. H. Quirk, and P. W. Jones)

Summary. The Airways Questionnaire-20 (AQ-20) is a short version (20 items) of the SGRQ. The AQ-20 is a unidimensional scale; no domain subscores are suggested. Of the 20 items, at least 6 appear to measure symptoms (eg, breathlessness and coughing attacks), 5 appear to measure health status (eg, difficulty engaging in activities because of symptoms), 5 to assess emotions related to symptoms (eg, worry and restlessness), and 4 QOL, more narrowly defined (eg, bother and cannot enjoy a full life). The instrument employs yes/no responses rather than a Likert scale, making it very simple and quick to administer (2-3 minutes). There is no cost for using this instrument, but permission must be obtained from the authors.

With respect to rationale and construct validity, the authors sought to develop a brief instrument with low respondent burden that could be used in clinical practice with patients with either asthma or COPD and that was minimally influenced by demographic variables, such as age, sex, and disease duration. They employed a criterion-based process of item selection and reduction that utilized both patient perceptions and factor analysis. There is evidence for the instrument's concurrent validity: The AQ-20 total score correlated significantly with generic QOL instruments (SF-8), perceived stress, and asthma severity, as well as depression and anxiety; with 7 of 8 SF-36 scales; with LWAQ and AQLQ scales; and with SGRQ. Sample demographics are not available in all published studies, but a recent US study sample using the AQ-20 was predominantly white and relatively well educated; a recent UK study sample was 50% South Asian; and the instrument has recently been used in Japan and Finland. With respect to responsiveness, there is evidence that the AQ-20 is able to detect within-subject changes over time. Change in AQ-20 was correlated with change in total and all subscale scores for SGRQ and the AQLQ developed by Juniper. An MCID has not been established for the instrument.

Strengths and weaknesses. The advantage to the AQ-20 is that it is a significantly shorter version of the well-established SGRQ; however, the AQ-20 has less published evidence of use in clinical research than the SGRQ. Limitations include the lack of subscores to distinguish patient perception of the impact of asthma on QOL from the large proportion (11/20) of questions that relate to health status or functional status.

Recommendation. The subcommittee recommends classifying the AQ-20 as a supplementary instrument for asthma clinical research in which the breadth of domains used in the SGRQ is desired but brevity is required, recognizing that the number of items measuring patient perception of the impact of asthma on QOL is limited.

ASTHMA-RELATED QOL INSTRUMENTS FOR PEDIATRIC STUDY POPULATIONS

QOL instruments developed for adults are not appropriate for use with children. There are several special considerations in developing pediatric instruments that have been described as the "4 Ds of childhood": developmental change, dependence on adults, different disease epidemiology from adults, and demographic characteristics unique to childhood.[10] Because of these challenges, pediatric QOL instruments are relatively less developed than adult instruments, but a growing number of pediatric instruments are available.[11]

Researchers should consider 2 interrelated key questions. First, will data be obtained from the child directly or from a proxy respondent (typically a parent)? For children who are too young or too ill to respond, parents are often the only logical informants. However, parents and children may have different views on the impact of disease, and some attributes of health, such as emotional distress, are difficult for parents to observe. Parental assessments also may be incomplete because most school-aged and older children are away from their parents for

many hours each day. Thus there is consensus that, as appropriate, children should report on their own health[12] and that, whenever possible, information about QOL should be obtained from both the parent and the child.[11] The second question for researchers to consider is whether the instrument has been developed and tested for the child age group in their study. Pediatric instruments should be tested with large and diverse enough samples to assess performance by age categories. Children's developmental capabilities shape their understanding of health. The dimensions of QOL may be less differentiated for the younger child. In very young children the measurement of QOL may be limited to whether the child is temporally upset, frustrated, angry, frightened, and/or hurting as the result of asthma. Asking children younger than 10 years of age to make complex, qualitative judgments about their QOL may well be beyond their developmental capabilities. Thus pediatric questionnaires for young children and those that span a large age range must be interpreted with caution. As they grow older, children are more likely to comprehend more abstract concepts related to QOL. A related consideration is mode of administration and available study resources; collecting data from children generally takes more time, and collecting data from younger children may require interviewer administration. Researchers should obtain QOL data in pediatric studies, but they need child-friendly and child-appropriate study design and instruments appropriate for administration to children or their parents.

Summary reviews of 4 pediatric asthma QOL instruments follow. Not included in this review are the Childhood Asthma Questionnaires, which were originally developed in 3 different forms for children of different age ranges (form A for children aged 4-7 years, form B for those aged 8-11 years, and form C for those aged 12-16 years). These instruments are not currently available for general use.

Child Health Survey for Asthma (developed by the American Academy of Pediatrics)

Summary. The Child Health Survey for Asthma (CHSA) is a paper-and-pencil instrument completed by parents of children aged 5 to 12 years with chronic asthma. It takes 20 minutes to complete. The CHSA was designed to enable children with asthma and their parents to provide input on how the children view their QOL. The instrument includes a broad spectrum of 48 child- and family-focused items divided into 5 subscales (physical health, 15 items; activity [child], 5 items; activity [family], 6 items; emotional health [child], 5 items; and emotional health [family], 17 items). For each of the 5 scales, computed scores are transformed, giving each scale a minimum score of 0 and a maximum score of 100. For all CHSA scales, higher scores indicate more positive outcomes or better health status. There are specific questions that refer to the way a child's degree of impairment affects either the child or the family. For example, questions about family activity include, "We changed family plans or trips because we were not sure when an attack could occur," "We canceled social plans because our child had a problem with asthma," and "We avoided activities or places that might trigger an attack (such as visits to the zoo or a farm, camping, or going outside in the cold)." The responses are "all of the time," "most of the time," "some of the time," "little of the time," and "none of the time." The questions about the emotional health of the child and the emotional health of the family also can refer to how much the degree of impairment due to asthma matters to the child and family. The CHSA yields 5 subscale scores (physical health, child activity, family activity, child emotional health, and family emotional health), with limited data on the MCID for just 1 subscale.

In developing the instrument, the researchers based initial items on comments from an American Academy of Pediatrics workgroup, parent focus groups, and parent cognitive interviews. The initial version of the CHSA had 71 questions, which were reduced to 48 items on the basis of several studies and specific elimination criteria (eg, low expert review rating, high ceiling effect, and correlation and covariance with other items). In addition, content validity, internal consistency, and test-retest reliability have been assessed through a series of studies.

Strengths and weaknesses. The strengths of the CHSA are that the instrument is freely available and has well-defined psychometric properties. Perceived impact of asthma on QOL might be inferred from the family activity subscale (changes in family activities because of the child's asthma), the child emotional health subscale (child's frustration and upset related to asthma and asthma treatments), and the family emotional health subscale (bother associated with asthma management, frustrations, concerns and worries, and stress for the family because of the child's asthma). The instrument has been used in socioeconomically and ethnically diverse populations within the United States, and a version for Spanish-speaking US residents has been developed. In addition, there is an accompanying version of the CHSA that can be completed by the child (CHSA-C). Weaknesses include limited published data on population norms.

Recommendation. The subcommittee recommends classifying the CHSA as a supplementary instrument, recognizing that much of the content (20 of the 48 items) includes functional status and health status and may overlap with that of measures of asthma control.

Child Health Survey for Asthma-Child Version (developed by the American Academy of Pediatrics)

Summary. The Child Health Survey for Asthma–Child Version (CHSA-C) is an asthma-specific QOL instrument administered to children, requiring an average of 10 minutes to complete, depending on the child's age; it is based on the CHSA, which is administered to caregivers. The CHSA and CHSA-C may be used as stand-alone or companion instruments.

The 25 items include 3 scales: physical health (7 items), child activities (6 items), and emotional health (12 items). The 7 items on physical health focus on asthma symptoms. The 6 items on child activities address asthma-related limitations in school, play, and sports. The items about emotional health include 8 questions focused on feelings about asthma and 4 items about stress, frustration, anger, and knowledge about asthma medications. For example, items include "My asthma causes stress in my family," "I am frustrated that other people don't understand what it is like to have asthma," and "Sometimes I get angry and ask 'why is this happening to me?'" Responses are "strongly disagree," "disagree," "not sure," "agree," and "strongly agree." The items that focus on emotional health, stress, frustration, and anger may reflect the degree to which impairment from asthma matters to the child, as well as the child's perception of the effect on the

family. For each scale, scores are transformed to a scale of 0 to 100, with 100 being most positive.

Items for the CHSA-C were developed based on intensive individual interviews with children, as well as expert review. The authors have published a description of the "psychometric properties of the CHSA-C, descriptive statistics, reliability (internal consistency and test-retest reliability), validity, and differences in performance characteristics by selected covariates (eg, child sex, race/ethnicity, and household income)."

Strengths and weaknesses. Strengths include appropriateness for use by children aged 7 to 16 years. Weaknesses of the CHSA-C include limited published psychometric properties, lack of population norms, overlap in content with measures of asthma control regarding the assessment of symptoms and functional status, and relative lack of use in the published literature. However, this is a relatively new instrument (2008).

Recommendation. The subcommittee recommends classifying the CHSA-C as an emerging instrument that requires further investigation and evaluation.

Pediatric Asthma Quality of Life Questionnaire (developed by E. F. Juniper)

Summary. The Pediatric Asthma Quality of Life Questionnaire (PAQLQ), developed in the mid-1990s by Juniper and colleagues, is a 23-item, child-reported instrument of the problems (physical, emotional, and social) most troublesome to children with asthma. It requires 10 to 15 minutes to complete. The instrument in use today also may be found under the name Standardized PAQLQ. There is no cost for using the PAQLQ in noncommercial research or practice; there is, however, a fee for commercial use. Copyright restrictions apply to all uses.

To develop the original content, a list of 77 candidate items was generated from a variety of sources, including interviews with health professionals, a review of the literature, and interviews with children and parents, who were encouraged to suggest aspects of their asthma that imposed a burden on them, including emotional and physical effects. One hundred Canadian pediatric asthmatic patients were then interviewed to rate the frequency and importance of the 77 candidate items. The resulting instrument includes symptoms (eg, feel out of breath and trouble sleeping). About half the symptom items might be considered to assess QOL because they assess the extent to which the symptoms bother the child. Also measured are activity limitations and emotional impact (eg, feeling left out because of asthma and feeling frustrated because of asthma). An overall PAQLQ score is calculated, as are 3 domain subscales: symptoms (10 items), activity limitations (5 items), and emotional function (8 items). All items use a 7-point Likert response scale (eg, 1 = extremely bothered; 7 = not bothered) with a 1-week recall period. The overall PAQLQ score is the mean of all 23 items, and the individual domain scores are the means of the items in each domain.

Strengths and weaknesses. The PAQLQ is a relatively short instrument designed for children (aged 7-17 years) to report on their own experiences. The instrument includes symptoms of asthma, as well the child's emotional reactions to the symptoms and limitations caused by asthma. The developers advise using the interviewer-administered version of the PAQLQ for all children younger than 11 years. The PAQLQ demonstrates good measurement properties (eg, internal consistency and test-retest reliability, plausible cross-sectional associations with other measures, and responsiveness to change and group differences). Weaknesses include the fact that age-specific psychometric information about the PAQLQ is limited, and this wide age range crosses several important developmental stages. Furthermore, information on the discriminative validity of its subscales is unavailable. The social and economic diversity of the original sample is unknown, although the instrument has subsequently been used in many pediatric asthma studies of diverse populations in many countries and is available in multiple languages. Furthermore, the PAQLQ reading level is not documented.

Recommendation. The subcommittee recommends classifying the PAQLQ as a supplemental instrument for pediatric studies, recognizing the limitations noted above, particularly the predominance of items related to health status and functional status and potentially limited ability to yield a distinct measure of the perceived impact on QOL, as well as the wide age range the instrument expects to cover.

Pediatric Asthma Caregiver Quality of Life Questionnaire (developed by E. F. Juniper)

Summary. The Pediatric Asthma Caregiver Quality of Life Questionnaire (PACQLQ), published in the mid-1990s by Juniper and colleagues, was designed to measure the impact of the child's asthma on the QOL of the caregivers (typically, parents). It takes 3 to 5 minutes to complete. There is no cost for using the PACQLQ in noncommercial research or practice; there is, however, a fee for commercial use. Copyright restrictions apply to all uses. In instrument development items were generated through literature review, discussion with health professionals, and unstructured interviews with parents of children with asthma. One hundred primary caregivers were then asked to rank the resulting 69 candidate items in terms of frequency and burden. The final instrument contains 13 items divided between activity limitations (eg, interference with work or sleep) and emotional function (eg, upset due to child's symptoms and worry over medication side effects). Respondents were asked to assess how, during the past week, their children's asthma had interfered with their normal daily activities and how this made the caregivers feel. An overall PACQLQ score was calculated, as well as 2 domain subscales: activity limitations (4 items) and emotional function (9 items). All items use a 7-point Likert response scale (eg, 1 = "very worried"; 7 = "not worried") with a 1-week recall period. The overall PACQLQ score is the mean of all 13 items, and the individual domain scores are the means of the items in each domain subscale.

Strengths and weaknesses. The strengths of the PACQLQ include that it is a short, readily administered instrument for assessing the impact of asthma on caregivers' and not children's QOL. In addition, the PACQLQ was originally tested on a small (n = 52) Canadian sample of parents and was able to detect changes in both the activity and emotional domains among parents who reported that their child's asthma status had changed. The social and economic diversity of the original sample is unknown, although the instrument has subsequently been used in many pediatric asthma studies of diverse populations and is available in multiple languages. Its limitations include potential overlap with measures of asthma control and the small sample size of the parent group on which the instrument was tested.

Recommendation. The subcommittee recommends classifying the PACQLQ as a supplemental instrument for pediatric studies when understanding the effect of a child's asthma on caregivers is of importance. However, researchers should consider the potential overlap between instrument content and measures of asthma control and also that the instrument only assesses the impact of the child's asthma on the caregiver in terms of the emotional and activity domains (ie, not economic, social, or other domains).

Pictorial Quality of Life Measure for Young Children With Asthma (developed by R. S. Everhart and B. H. Fiese)

Summary. The Pictorial Quality of Life Measure for Young Children With Asthma (Pictorial PAQLQ) is a new asthma-specific QOL instrument for children adapted from the PAQLQ that was developed by Juniper. Information on time required to complete this instrument was not reported. It includes 2 subscales: symptoms (10 items) and emotions (5 items). The items in the symptoms subscale focus on how frequently symptoms such as cough and wheeze and difficulty sleeping bother the child. The emotional scale inquires about feelings of worry, anger, and crankiness because of asthma. The activities subscale that is part of the original PAQLQ is not included in this version.

This instrument was designed for pencil-and-paper administration for children with asthma aged 5 to 7 years. It is administered by an interviewer, with pictorial representations to allow for developmentally appropriate reporting directly from young children. The pictorial response format allows the child to anchor his or her response decisions among 3 thermometers, which are empty, half-filled, and filled, to represent "none," "some," or "all of the time." Children are asked to rate their response to each item anywhere on a line below the 3 thermometers, and a scoring template is used to score responses on the line. The range of values is 1 (empty thermometer) to 7 (full thermometer). Subscale scores are calculated from the mean of responses for each subscale, and total QOL is calculated from the mean of all responses.

Initial testing included a confirmatory factor analysis and validity testing with a diverse sample of 101 children with asthma. Convergent validity was assessed by correlating scores with children's FEV_1 and caregiver scores on the PACQLQ. Discriminant validity of the total score was assessed by comparing scores with measures of children's verbal ability. Predictive validity was assessed by comparing scores on the instrument with later scores on the PAQLQ for a subset of children at 8 years of age ($n = 48$ for the longitudinal assessment).

Strengths and weaknesses. The Pictorial PAQLQ holds promise as a new instrument for direct reporting of QOL from young children. This is particularly important because young children can provide information that is distinct from that obtained from their caregivers, and few instruments currently are available for this age group. Initial testing of this instrument suggests adequate psychometric properties and provides preliminary evidence of convergent, discriminant, and predictive validity for the overall score. The instrument was developed with specific attention to the cognitive abilities and developmental status of young children. Its limitations include that no discriminant validity information is available for the subscores. In addition, further testing to confirm the proposed factor structure and provide further validation is needed.

Recommendation. The subcommittee recommends classifying this instrument an emerging instrument for use in clinical research.

Pediatric Quality of Life Inventory 3.0 Asthma Module (of the Pediatric Quality of Life Inventory) (developed by J. W. Varni)

Summary. The Pediatric Quality of Life Inventory 3.0 Asthma Module (PedsQL 3.0 Asthma Module) is 1 of many disease-specific modules that are part of the Pediatric Quality of Life Inventory (PedsQL). The PedsQL Measurement Model uses a modular approach, with generic and disease-specific scales. It is noteworthy that the generic QOL Module and not the Asthma Module contains the QOL questions. The PedsQL 3.0 Asthma Module is combined with this generic QOL instrument. The Asthma Module collects additional information regarding social relations, worry, and specific asthma treatment issues; however, it does not measure the child's or caregiver's perception of the impact of asthma on the child's QOL. Information on the time required to complete this instrument was not reported.

The asthma module is designed for children and adolescents aged 2 to 18 years. There are a version for parent report on toddlers (aged 2-4 years) and versions for parent report and child report for young children (5-7 years), children (8-12 years), and teens (13-18 years).

In the disease-specific Asthma Module, there are 4 scales (asthma symptoms, 11 items; treatment problems, 11 items; worry, 3 items; and communication, 3 items). The treatment-problem questions are difficult to categorize in Table IV. These range from "Do your medicines make you feel sick?" to "Do you have trouble using your inhaler?" to questions about adherence, such as "Do you refuse to take your medicines?," to questions about being scared, such as "Do you get scared when you have to go to the doctor?" As a result, the PedsQL 3.0 Asthma Module focuses more on assessment of asthma symptoms and problems than on general QOL. The questions were based on previous experience with the generic PedsQL, focus groups, cognitive interviews, pretesting, and field testing. A 5-point scale is used. Items are reverse scored and linearly transformed to a 0- to 100-point scale ($0 = 100$, $1 = 75$, $2 = 50$, $3 = 25$, $4 = 0$); higher scores indicate better QOL. For self-report by a young child, a simplified 3-point scale is used ($0 =$ "not at all a problem," $2 =$ "sometimes a problem," and $4 =$ "a lot of a problem"). Reliability and validity have been assessed in several different studies.

A modified version of the PedsQL 3.0 Asthma Module, called the PedsQL 3.0 SF22 Asthma Module, includes questions about asthma symptoms (eg, problems with asthma symptoms, 11 items) and treatment problems (eg, problems with medicines or inhalers, 11 items). These 2 components were considered to be most relevant and were retained in the PedsQL 3.0 SF22 Asthma Module. These scales have demonstrated reliability (Cronbach's $\alpha \geq 70$) and validity in previous analyses.[13]

Strengths and weaknesses. Although the PedsQL core instrument is well defined and versions for 3 different age groups were developed, the psychometric properties of the asthma module instrument are still emerging. Weaknesses include the fact that the instrument's questions are dominated by questions of

TABLE III. Summary of adult QOL instruments

	ABP	AIS-6	AQLQ	AQLQ-S	Mini-AQLQ	LWAQ	AQLQ-Marks	M-AQLQ-Marks	ASF	SGRQ	AQ-20
Author/developer											
	Hyland (mhyland@plymouth.ac.uk)	Kaiser Permanente and Quality Metrics, Inc (www.qualitymetric.com)	Juniper (www.qoltech.co.uk)	Juniper (www.qoltech.co.uk)	Juniper (www.qoltech.co.uk)	Hyland, Dann, & Finnis	Marks	Marks	Integrated Therapeutics Group & Quality Metrics, Inc	P. W. Jones (www.healthstatus.sgul.ac.uk)	Barley, Quirk, & Jones (www.healthstatus.sgul.ac.uk)
Domains covered											
Symptom frequency			12 items	12 items	5 items	2 items			5 items	8 items (symptom subscale)—re: frequency, intensity, and duration	7 items
Perceived functional limitations									5 items	26 items (impact subscale)	1 item
Participation in normal activities	3 items	4 items	11 items (5 based on self-identified activities)	11 items (5 based on standardized activities)	4 items (based on standardized activities)	Measured across many domains: sport, 3 items; holidays, 3 items; sleep, 4 items; work, 6 items; mobility, 6 items; and colds, 5 items	9 items	11 items		16 items (activity subscale)—how problems affect, or are affected by, activities	4 items
Tolerance of physical environment			4 items	4 items	3 items	1 item	1 item	1 item			
Social relations	2 items	1 item				6 items	4 items	4 items		Included in Impact subscale	3 items
Mood and emotional well-being	4 items	1 item	5 items	5 items	3 items	22 items	5 items	5 items	3 items	Included in Impact subscale	3 items
Perceived risk/fear	2 items					4 items	6 items	6 items		Included in Impact subscale	
Health and longevity	3 items					9 items	2 items	2 items	2 items	Included in Impact subscale	1 item
Financial well-being	1 item									Included in Impact subscale	
Bother	15 items (all of the above)					Included across several domains				Included in Impact subscale	1 item
Total no. of items	22 items (15 bother, 7 management)	6 items	32 items	32 items	15 items	68 items*	20 items*	22 items*	15 items	50 items	20 items
Instrument characteristics											
Response format	Two 6-point Likert scales	Two 5-point Likert scales	Four 7-point Likert scales	7-point Likert scale	7-point Likert scale	4-point Likert scale	5-point Likert scale	7-point Likert scale	5-point Likert scale	Yes/no and ordinal response options	Dichotomous: yes/no
Intended use	Clinical research	Clinical research	Clinical research, patient monitoring	Clinical research, patient monitoring	Clinical research, patient monitoring	Clinical trials	Clinical research, patient monitoring	Clinical research, patient monitoring	Clinical research, patient monitoring	Clinical research	Clinical research
Target population	Adults	Adults	Adults	Adults	Adults	Adults	Adults	Adults	≥14 y	Adults	Adults

(Continued)

TABLE III. *(Continued)*

	ABP	AIS-6	AQLQ	AQLQ-S	Mini-AQLQ	LWAQ	AQLQ-Marks	M-AQLQ-Marks	ASF	SGRQ	AQ-20
Time to complete	10 min	3 min	5-15 minutes	5-15 minutes (4-5 minutes according to Qoltech Web site)	3-4 min	15-20 minutes	<5 min	NA; probably <5 min	NA; probably 3-4 min	8-15 min	2-3 min
Patient report	Patient	Patient	Patient	Patient	Patient	Patient	Patient	Patient	Patient	Patient	Patient
How is it administered?	Self	Self, interviewer, paper and pencil, fax, telephone, PDA, IVR	Self, interviewer, online, electronic devices	Self, interviewer, online, electronic devices	Self, interviewer	Self	Self, telephone interview	Self	Self	Self, telephone interview, online, computer-based	Self
Recall period	None	4 weeks	2 weeks	2 weeks	2 weeks	None	4 weeks	4 weeks	4 weeks	Varies: 4 weeks, 3 months, or 1 y	None
Reading level	NA	NA	NA	NA	NA	NA	>Grade 5	>Grade 5	Grade 4.8	NA	NA
Languages in addition to English	Japanese, Norwegian	Spanish	>20	>20	>20	Danish, Dutch, Finnish, French, German, Italian, Japanese, Korean, Norwegian, Spanish, Swedish, possibly Croatian	Spanish, Norwegian, Portuguese, French, Punjabi	NA	Spanish, Chinese-American	>20	Chinese, Dutch, Portuguese for Brazil, Swedish, Japanese, Russian, Spanish, Finnish
Cost to use	Free. Contact M. E. Hyland for permission to use.	Fee, but amount unknown.	Free for noncommercial clinical practice and research. Contact E. Juniper for permission to use. Otherwise, there is a 1-time fee.	Free for noncommercial clinical practice and research. Contact E. Juniper for permission to use. Otherwise, there is a 1-time fee.	Free for noncommercial clinical practice and research. Contact E. Juniper for permission to use. Otherwise, there is a 1-time fee.	Unknown. Appears to be free.	NA	NA	NA	Free for noncommercial clinical practice and research. Otherwise, there is a license fee.	No cost, but permission must be obtained from the authors.
Scoring method	Paper and pencil; total score and scores for 2 domains: distress, asthma management.	Self- or computer-scored. No domain subscores are suggested.	7-point scale for each domain. Overall score is mean of all 32 items (range, 1-7). Domain scores are mean of specific domain items (range, 1-7). 4 domains: symptoms, activity limitation, emotional function, and environmental exposures.	7-point scale for each domain. Overall score is mean of all 32 items (range, 1-7). Domain scores are mean of specific domain items (range, 1-7). 4 domains: symptoms, activity limitation, emotional function, and environmental exposures.	7-point scale for each domain. Overall score is mean of all 32 items (range, 1-7). Domain scores are mean of specific domain items (range, 1-7) 4 domains: symptoms, activities, emotions, and environmental exposures.	Scored as overall score; construct scores for problems and evaluation; construct scores for activities, avoidance, distress, and preoccupations; or 11 domain scores.	Items scored from 0 to 4. Subscale scores = mean of subscale items × 2.5 (resultant scores range from 0 to 10, with higher scores indicating poorer QOL). Subscales are breathlessness, mood, social, and concerns. Total score = mean of 4 subscale scores.	Unlike the original AQLQ-Marks, items are not transformed, so higher scores indicate less impairment. Yields total score and subscale scores for breathlessness, mood, social, and concerns. Subscale scores = mean of all the items in that domain. Total score = mean of all items.	Likert method of summated ratings. Yields a total score and 5 subscale scores: SFI (5 items), FWA (5 items), PIA (3 items), asthma energy (1 item), and asthma-confidence in health (1 item).	Computer scored; scoring algorithm available online. 3 subscales: symptoms, activity, and impact.	Items are marked as "yes," "no," or "not applicable." Positive responses only are summed to provide a total score out of 20. Unidimensional; no domain subscores are suggested.

(Continued)

TABLE III. *(Continued)*

	ABP	AIS-6	AQLQ	AQLQ-S	Mini-AQLQ	LWAQ	AQLQ-Marks	M-AQLQ-Marks	ASF	SGRQ	AQ-20
Psychometric testing											
Reliability	In Norwegian sample, internal consistency: Cronbach's α = 0.92-0.93. Test-retest: r = 0.76-0.88.[4]	Cronbach's α = 0.95.[14]	Internal consistency: NA in recent North American studies. In Spanish sample, Cronbach's α for overall score = 0.96, symptoms = 0.95, activity = 0.83, emotions = 0.84, environment = 0.78.[15,16] High concordance between electronic and paper versions, overall score ICC = 0.99, ICCs for 4 domains 0.97-0.99.[17] Test-retest: ICC = 0.95 in Canadian sample.[18] In Spanish sample, ICC for overall score = 0.90, symptoms = 0.82, activity = 0.92, emotions = 0.86, environment = 0.86.[15,16]	Internal consistency: Cronbach's α = 0.96 for overall score in US sample.[19] In English-speaking Singapore sample, α = 0.97 for overall score, 0.95 for symptoms, 0.80 environment, 0.88 emotions, 0.89 activities.[20] In Swedish sample, overall α = 0.93, domains 0.75-0.94.[21] (Consistency between paper and electronic adminis-trations, ICC = 0.90-0.95 for domains, 0.96 overall.[19]) Test-retest: ICC = 0.96.[22] For electronic version, 1-week ICC = 0.88 for overall score, 0.90 for activity limitation, 0.87 for symptoms, 0.81 emotional function, 0.85 environmental stimuli.[19] In English-speaking Singapore sample, ICC = 0.97 for overall score, 0.95 for symptoms, 0.88 environment, 0.94 emotions, 0.94 activities.[20] In Swedish sample, overall score = 0.95, domains 0.81-0.90.[21]	Internal consistency: Cronbach's α = 0.80-0.89 across scales.[23] In Swedish sample, overall Cronbach's α = 0.93, α for domains ranged from 0.68 to 0.87.[21] Test-retest: ICC = 0.79-0.83 for overall index and 3 of 4 subscales, activity subscale ICC = 0.72.[23] Swedish overall test-rest reliability was 0.86, with reliability for domains 0.78-0.83. (High concordance between mail-in and supervised completion, ICC = 0.96.[24])	Internal consistency: Cronbach's α for total score is very high in US and Norwegian samples: = 0.97.[4,25] Cronbach's α high for problems = 0.94; evaluations α = 0.90; and for dysphoric states and attitudes domain = 0.93. Most other domains α > 0.70, except social (α = 0.63) and medication usage (α = 0.57-0.67).[4,25] Test-retest: High in US/UK (r = 0.90-0.95) and Norwegian samples (r = 0.95).[4,26] Good in Japanese sample (r = 0.81).[27]	Internal consistency: Cronbach's α for total score = 0.92-0.95. Subscales: breathless-ness = 0.86-0.89, mood = 0.82-0.85, social = 0.88-0.91, concerns = 0.84-0.89.[28,29] Test-retest: ICC for total score = 0.80. Subscales: breathless-ness = 0.61, mood = 0.78, social = 0.78, concerns = 0.80.[29]	Internal consistency: Cronbach's α for total score = 0.97. Subscales: breathless-ness = 0.95, mood = 0.90, social = 0.96, concerns = 0.92.[30] Test-retest: ICC for total score = 0.93. Subscales: breathless-ness = 0.91, mood = 0.88, social = 0.93, concerns = 0.91.[30]	Internal consistency: Cronbach's α = 0.88-0.93 for total score. Subscales: SFI α = 0.78-0.84, FWA α = 0.85-0.90, PIA α = 0.79-0.90.[31] Total and 3 subscale α values exceed minimum 0.70 level for group comparison, and are at or near the 0.90 minimum recommended for instruments used to evaluate clinical change in individuals. Test-retest: ICC = 0.89 for total score, 0.72-0.90 for subscales.[32]	Internal consistency: NA in asthma studies since 2000 in English-speaking samples. In Spanish sample, Cronbach's α for overall score = 0.86, symptoms = 0.70, activity = 0.88, impacts = 0.82.[16] In Taiwan, α = 0.93, 0.82, 0.88, and 0.87, respective domains noted above.[33] Test-retest: Spearman's rho = 0.90 for total, 0.85 for symptoms, 0.83 for activity, and 0.88 for impacts subscales, over 2 weeks.[34] In Spanish sample, 2-week ICC for overall score = 0.94, symptoms = 0.82, activity = 0.91, impacts = 0.91.[16] Reliability data are also available for Moroccan sample of asthma and COPD patients.[35] (Results provided are for asthmatic patients only; there are many more COPD studies.)	Internal consistency: Cronbach's α = 0.81-0.92. Test-retest: 2 weeks apart, r = 0.93,[36] 6 months apart, r = 0.72.[37]

(Continued)

TABLE III. *(Continued)*

	ABP	AIS-6	AQLQ	AQLQ-S	Mini-AQLQ	LWAQ	AQLQ-Marks	M-AQLQ-Marks	ASF	SGRQ	AQ-20
Validity	In Norwegian sample, ABP highly correlated with LWAQ (r = 0.89), moderately correlated with state and trait anxiety, 6MWD.[4] In Japanese sample, ABP total scores correlated with depression and anxiety, all SF-36 subscales, and all LWAQ and AQLQ subscales.[5] Content and construct validity: scale formed using previous scales and focus group feedback.	The AIS-6 is strongly correlated with the total Mini-AQLQ (r = 0.84) score, as well as the activity (r = 0.82) and symptoms (r = 0.78) subscales (all $P < 0.0001$). Also, AIS-6 total score was correlated with Mini-AQLQ emotions (r = 0.70) and environment (r = 0.54) subscales. Convergent validity: AIS-6 scores were significantly related to smoking, BMI, history of COPD, systemic corticosteroid use, and asthma hospitalization in past year ($P <$ 0.001). The AIS-6 total score was moderately to strongly correlated with general health rating (r = 0.52), ATAQ (r = 0.67), AOMS (r = 0.57), and self-severity rating (r = 0.69). Regarding construct validity, the item pool was developed according to a conceptual model for	Spearman's r = 0.64 vs ACQ, r = 0.20 vs PEF, r = 0.18 vs % predicted FEV_1, r = 0.03 vs SABA use.[18] Total AQLQ also significantly correlated with LASS symptom score (r = −0.68), SABA medication and albuterol use (r = 0.33, 0.37), SF-36 physical (r = 0.53-0.69 across 2 studies), SF-36 mental (r = 0.48-0.49 across studies), and the other SF-36 domains (r = 0.45-0.65); and all AQLQ subscales significantly correlated with all SF-36 subscales (r = 0.36-0.68).[18,38-41] Significant correlations of overall AQLQ score with other measures by asthma severity. For example: FEV_1, r = 0.18 for mild asthma although not significant for moderate-severe asthma; AM PEF, r = 0.18 for mild asthma and 0.13 for moderate-severe; PM PEF, r = 0.20 for mild, and 0.13 for	Correlations with overall score r = 0.62-0.74 (across studies) vs ACQ, r = 0.19-0.40 (across studies) vs PEF, r = 0.21-0.38 (across studies) vs % predicted FEV_1, r = 0.05 vs SABA use, r = −0.30 for no. of admissions, r = −0.26 for no. of asthma medications, r = −0.43 with depression scores (HAD).[22,50,51] Subscale correlations for each domain are comparable to those for overall score (see Tan et al, 2004,[20] Singapore study). There is also strong evidence for concurrent validity in international samples in Denmark and Sweden.[21,52] See AQLQ column for rationale.	Cross-sectionally, the Mini-AQLQ has similar validity to AQLQ. Longitudinally, the Mini-AQLQ is not as good as the AQLQ at measuring change in QOL. Correlations between Mini-AQLQ and full AQLQ ranged from 0.81 to 0.90 overall and for 3 of 4 subscales, but was only 0.63 for activity subscale.[23] Item functioning is similar for English and Spanish versions, and in Latino and black samples, although measure may have 3-factor structure in these minority samples.[53] A factor analysis of several asthma QOL measures identified that the 2 most prominent factors, asthma symptom frequency and asthma symptom bother, were captured by the Mini-AQLQ.[54] In a Swedish sample, correlations between Mini-	In US sample, total LWAQ significantly associated with subjective illness severity (r = 0.48), objective illness severity (r = 0.33), anxiety (r = 0.50), and depression (r = 0.31).[55] In UK samples, total LWAQ score has good convergent validity (r = 0.66 with SIP) and predictive validity (r = 0.35 with corticosteroid prescribing, r = 0.44 with PEF).[26] Worse LWAQ scores in patients with poor compliance.[56] In Norwegian sample, LWAQ total score was significantly correlated with ABP score, state and trait anxiety, and 6MWD.[4] In Japanese sample, LWAQ total score and activities, avoidance, distress, and preoccupation scales were all significantly associated with ABP and AQ-20 scores. LWAQ total score also was associated with global QOL and	AQLQ-Marks total score correlated with asthma medication use, unemployment due to asthma, asthma symptom level, depressive symptoms, BMI, general physical function, and VLA function. Correlations with other markers of severity, such as FEV_1, were in the expected direction but not significant.[29,63-68] Regarding subscales, total score and all 4 subscale scores were associated with workplace exacerbation of asthma, smoking status, and asthma medication use. Breathlessness, concerns, and social scales correlated with corticosteroid use (ie, not mood subscale), but hospitalization correlated with concerns subscale only.	Total score and all 4 subscale scores significantly correlated with symptoms, medication use, FEV_1, global health rating, and all SF-36 subscales. Total score also was associated with clinical asthma status by NAEPP severity criteria. Regarding predictive validity, total score and all 4 subscale scores predicted hospital admission and ED visits for asthma over the 12-month study period.[30,69,70]	Concurrent: All ASF scales were predictive of global patient-rated severity, NAEPP severity classification, and no. of missed work days, with the ASF total score having greater validity than the AQLQ-Marks regarding the breathlessness scale and for the total score predicting the NAEPP severity classification and missed work days, and for predicting patient-rated severity.[31] The ASF SFI was the strongest predictor of NAEPP asthma severity and workdays missed. The other scales showed significant but slightly lower predictive power.[31] Better baseline total scores were associated with lower risk of an asthma-related ED visit or hospitalization and decreased asthma-related costs during 1-year follow-up. Better FWA subscale scores were associated	Significant correlation between total score and presence of cough, sputum, and wheeze; health status; asthma severity; symptom frequency; FEV_1; dyspnea; and physician contact. Total scores also correlated with other asthma QOL scales: AQLQ-Juniper, AQ-20, LWAQ; as well as the SF-36. Regarding subscales, significant correlation between other measures of disease activity (lung function -FEV_1, FVC, PEF, oxygen saturation at rest; 6MWD; MRC dyspnea grade; anxiety score, depression score, SIP total score, SIP physical domain, SIP psychosocial domain, smoking, ED visits, hospital admissions) and SGRQ symptom, activity, and impact domains. Evidence of validity from studies in the US, UK, Australia, Finland,	Significantly correlated with other QOL measures: all AQLQ-Juniper (r = −0.40-0.80) and SGRQ (r = 0.46-0.86) scales, and total AQLQ-Marks (r = 0.85).[65,83] Significantly correlated with clinical indicators such as PEF (in some but not all studies), asthma severity, asthma impact, sleep disturbance, and bronchodilator use.[37,83] AQ-20 prospectively predicted asthma exacerbations during 6-month follow-up.[37] In Japanese samples, AQ-20 total significantly correlated with generic QOL (SF-8), perceived stress, and asthma severity,[84] as well as depression and anxiety, 7/8 SF-36 scales, and all LWAQ and AQLQ scales.[5] In a Finnish sample, AQ-20 was strongly correlated with SGRQ total (r = 0.86).[75] With respect to rationale and construct

(Continued)

TABLE III. *(Continued)*

ABP	AIS-6	AQLQ	AQLQ-S	Mini-AQLQ	LWAQ	AQLQ-Marks	M-AQLQ-Marks	ASF	SGRQ	AQ-20
	constructing health-related QOL measures for clinical outcomes. Research items were chosen using IRT analyses. All validity data are from Schatz et al (2007).[14]	moderate-severe; rescue puffs of SABA, $r = -0.49$ and not significant; shortness of breath, $r = -0.56$ for mild and -0.25 for moderate-severe; wheeze, $r = -0.50$ for mild and -0.21 for moderate; cough, $r = -0.34$ for mild and -0.27 for moderate.[40] Evidence for concurrent validity in international samples in Spain, Japan, and Portugal.[5,15,16,42-47] Regarding rationale and construct validity, items were generated through literature review, discussion with chest physicians, and patient interviews, and chosen by having patients rate which were most troublesome.[48] Factor analysis including items from AQLQ and measures of asthma clinical status identified asthma-specific QOL, as measured by the AQLQ, as a separate factor.[49]			AQLQ and AQLQ-S were strong ($r = 0.80$), except for the environmental domain ($r = 0.73$).[21]	well-being measures, FEV_1, anxiety, and depression. Pattern of correlations for all 4 subscales were similar.[5,57] In Korean sample, total LWAQ score associated with duration of asthma, hospital admissions, PEF, and recent symptoms.[58] There also was evidence for convergent validity with various asthma symptoms in Chilean sample,[59] and associations between LWAQ and depression and anxiety symptoms in German sample.[60] Rationale and construct validity: Item content was derived from focus groups of asthmatic patients, items selected based on their psychometric properties. Initial factor analysis indicated a unidimensional scale,[26] but later factor analyses supported the existence of 2-4 constructs.[61,62]			with a decreased risk of asthma-related ED visit/hospitalization during follow-up, but there was no predictive relation between other subscale scores and asthma-related utilization.[32]	Hungary, Japan, Morocco, Spain, and Taiwan.[5,15,16,33,35,43,44,47,71-81] It is unclear whether there is a theoretic rationale behind the measure, but the 3-subscale structure is supported by the results of principal components analysis.[82]	validity, the authors used a criterion-based process of item selection and reduction that utilized both patient perceptions and factor analysis.[36] An 18-item version is unidimensional, but 20-item version may be measuring >1 dimension.[34]

(Continued)

TABLE III. *(Continued)*

	ABP	AIS-6	AQLQ	AQLQ-S	Mini-AQLQ	LWAQ	AQLQ-Marks	M-AQLQ-Marks	ASF	SGRQ	AQ-20
Responsiveness (sensitivity to change). Referred to as "Respons. index"	Evidence that ABP scores change over time in UK and Norwegian samples.[4]	Within-subject changes over time have not been assessed. 1 study examined between-group changes in intervention vs control groups and found no group difference.[85] However, the groups did not differ on most other measures; so results may reflect the intervention more than the measure.	Able to detect within-subject changes over time and between-subject differences. Respons. index = 1.35.[18,86]	Able to detect within-subject changes over time and between-subject differences. Respons. index = 1.34.[22]	Able to detect within-subject changes. Respons. index = 0.97. Intervention studies using the Mini-AQLQ are able to detect changes in QOL over time.[87] In Swedish sample, Mini-AQLQ's responsiveness to change is similar to AQLQ-S.	In Japanese samples, changes in the mobility, medication usage, holidays, sport, work and other activities, and dysphoric states and attitudes subscales were observed as a result of treatment. However, the LWAQ was less responsive than both the AQLQ and the AQ-20.[45] A study in Malta provided evidence for change in total LWAQ score as a result of treatment.[88] Also, there was evidence for change over time in Swedish and German samples.[89,90] Recent studies in US samples have not provided evidence for the measure's responsiveness.	Able to detect within-subject changes in total score and all 4 subscale scores in response to treatment.[91] There were within-subject changes in total score in response to changes in general physical function, VLA function, symptom scores, and bronchial responsiveness.[65,66] Total score and mood and social subscales were able to differentiate between improved and stable subjects; breathlessness and concerns subscales were not.[92]	Able to detect within-subject changes in total score over time, and associations between changes in total score and changes in symptoms, FEV_1, self-rated severity, and medication use.	Over 8 weeks: RV % = 110% for change in % predicted FEV_1; RV% = 93% for 1-year change in NAEPP severity category; RV% = 84% for 1-year change in global, patient-rated asthma severity; and RV% = 89% for 1-year change in work days missed in the past 4 weeks. In addition to total score, SFI and FWA scores were responsive to changes in these criteria.[31] Over 1 year, ASF scores were responsive to changes in asthma severity, especially the SFI (improved patients had 0.60 SD change). The other subscales did not show statistically significant changes in response to changing severity.[93] Note: RV is referenced to scales of all 20 AQLQ-Marks plus 6 ITG physical and psychosocial symptom/side effect items.	Able to detect within-subject changes in total score over time, and associations between changes in total score and changes in other measures (eg, dyspnea, AQLQ scores).	Able to detect within-subject changes over time. Change in AQ-20 was correlated with change in total and all subscale scores for SGRQ and AQLQ-Juniper.[83] In a Japanese sample, AQ-20 was highly responsive after 6-month follow-up, but there was a ceiling effect. Change in AQ-20 was correlated with change in FEV_1 and total AQLQ and LWAQ.[45] Also able to detect change over time in a Finnish sample.
MCID	NA	NA	0.50 point,[94] but this is debated in the literature.[7] Critiques recommend a Number-Needed-to-Treat	0.50 point, but this is debated in the literature.[7] Critiques recommend a Number-Needed-to-Treat	0.50 point was established for the AQLQ and AQLQ-S, and has been adopted for the Mini-AQLQ as well. However,	NA	Katz et al (2004)[65] applied 2 methods of computing an MCID to the AQLQ-Marks, SEM and	0.50 point, established using Juniper methodology.[70]	NA	4 points for overall scale, and activity and impact subscales; no known MCID for symptoms	NA

(Continued)

TABLE III. *(Continued)*

	ABP	AIS-6	AQLQ	AQLQ-S	Mini-AQLQ	LWAQ	AQLQ-Marks	M-AQLQ-Marks	ASF	SGRQ	AQ-20
			analysis, using the 0.50-point increase criterion. For determining MCID, the use of the proportions of individual patients achieving a 0.50 improvement, rather than group mean improvement of 0.50, also has been suggested.[95]	analysis, using the 0.50-point increase criterion. For determining MCID, the use of the proportions of individual patients achieving a 0.50 improvement, rather than group mean improvement of 0.50, also has been suggested.[95]	the original methodology used to establish this value has been questioned.[7] Critiques recommend a Number-Needed-to-Treat analysis, using the 0.50-point increase criterion. For determining MCID, the use of the proportions of individual patients achieving a 0.50 improvement, rather than group mean improvement of 0.50, also has been suggested.[95]		Norman et al (2003)[96] method of using 0.5 SD difference as threshold. Using SEM method, MCID = 3.3. Found that 1 VLA affected was associated with 1.9 difference in AQLQ; so 2 VLAs affected would be an MCID. Using Norman's 0.5 SD method, MCID = 7.3; so 4 VLAs affected would result in MCID.			subscale.[97]	
Sample size(s) tested	n = 40-327.	n = 554 in validation study[14]; n = 6948 for intervention study.[85]	n = 30 in original study. Other studies' sample sizes range from 30 to 3000+, in recent studies n range = 40-763.	n = 40 in original study. Other studies' sample sizes range from 30 to 3000+, in recent studies n range = 55-3297.	n = 40 in development study. In other studies, n = 96-35450.	n = 783 in original study. In recent studies, n = 44-879.	n = 283 in development study. In recent studies, n = 78-743.	n = 293.	n = 142-269 in original study. Other studies' sample sizes range from 119 to 3482.	This instrument has been tested in numerous populations. In recent asthma studies, n ranged from 31 to 396.	n = 90 in validation study. In recent studies, n ranged from 135 to 695.
Sample characteristics: income/SES, race/ethnicity, country	NA	Patients in validation sample were older than 35 years (23% ≥ 65) and more likely to be white (91%), well educated (40% college grads), and nonpoor (48% had income ≥$50,000). Patients in intervention sample were middle-aged (M = 51.8, range 18-99), 65% female, predominantly white (92%).	Instrument has been used in international settings representing ethnically diverse populations, and among low-SES and ethnic-minority adults with asthma in US. Sample info is available from published studies.	Instrument has been used in international settings representing ethnically diverse populations, and among low-SES adults with asthma. Sample info is available from published studies.	Instrument has been used in international settings representing ethnically diverse populations, and among low-SES and minority adults with asthma. Has been used in samples with diverse ages (eg, Feifer et al, 2004[87] includes 27% younger than 18 years, 22% ≥ 65), but has not been validated for different age groups. Sample info is available from published studies.	Available from published studies about country, age range, and sex. Has been used in diverse international settings, including Germany, Norway, Japan, Korea, Malta, and Croatia, and in a low-income UK sample. However, it has not been used in ethnically/socioeconomically diverse US samples (predominantly upper middle-class, white).	Very little info is available. Many populations using this instrument have been quite homogeneous. Predominantly used in higher income and education samples. Most samples > 70% white, but 1 Canadian sample was >50% East Indian and 1 US sample 41% minority. Used in Australia and France, in addition to Canada and the US.	Instrument was validated in a socioeconomically diverse Australian sample.	Available from published studies about race/ethnicity, age, sex, and SES. Has been used in 6 published studies in both predominantly white and in broadly representative populations, but not in predominantly minority or low-income populations. Most studies have been conducted in the US.	Instrument has been used in a variety of settings presumably representing a broad range of populations, including studies around the world (US, UK, Australia, Finland, Hungary, Italy, Japan, Malaysia, Morocco, Netherlands, Norway, Spain, and Taiwan). However, most studies did not provide demographic info on income/SES or race/ethnicity.	Info NA in most published studies. A recent US study using the AQ-20 was predominantly white and well educated; in a recent UK study sample was 50% South Asian. Has also been recently used in Japan and Finland.

(Continued)

TABLE III. *(Continued)*

	ABP	AIS-6	AQLQ	AQLQ-S	Mini-AQLQ	LWAQ	AQLQ-Marks	M-AQLQ-Marks	ASF	SGRQ	AQ-20
Diversity of psychometric evaluations (different populations, methods of administr-ation, age groups, etc)	Norwegian and Japanese validation studies.	NA	Yes. Available directly from published studies in diverse US and international samples.	Yes. Available directly from published studies.	Swedish validation study.[21] Psychometrics available for black and Latino US samples.[53] Juniper's Web site indicates that Mini-AQLQ has been translated and culturally adapted for 21 countries in 12 languages, but psychometric data are not available for all samples. It does not indicate which samples psychometric info is available for.	Yes. Psychometric info is available from published studies based on US, UK, Norwegian, Japanese, and Korean samples. However, recent US studies have not used diverse samples (more than 90% white).	Psychometric info is available from published studies based on Australian and US samples.	No. All psychometric data are from an Australian sample.	Psychometric info is needed from more diverse samples. A pediatric version has been developed that is completed by parents.	Unclear whether validated (for asthma rather than COPD) in diverse US samples, but has been validated in different languages in samples around the world (see above).	Unclear, as validation studies present little demographic info. Validated in Japanese and Finnish samples.
Instrument summary											
Additional info needed.	Need info on psychometric properties in US sample; info on sample characteristics and population norms is not available.	Substantial proportion (22%) of patients with self-reported coexisting COPD, but we have no reason to believe that would influence the study results. Need evidence for test-retest reliability. Validity has not been tested in people younger than 35 years. Future studies should validate in younger samples. Also needs validation in more diverse samples (validation and	Need reliability and validity info for non-English translations and other versions. Need to validate in older adults (>65 years). Recent US studies have not provided reliability data.	Need reliability and validity info for non-English translations and other versions. Need to validate in older adults (>65 years). Need more research on ethnically and socioecono-mically diverse US samples.	Need reliability and validity info for non-English translations and other versions. Need to validate in older adults (>65 years).	Needs validation in more socioecono-mically and ethnically diverse US samples. Needs more info on responsiveness in US samples.	Need more studies to be done regarding AQLQ-Marks' utility as a discriminative measure (with regard to other clinical indices and asthma severity), and further research is needed on between- subject and within-subject variability. Its predictive capabilities also need to be assessed. Needs validation in more diverse samples.	Measure needs to be validated in diverse US samples.	Separate validation data for non-English-language versions of the ITG-ASF have not been published; nor were studies found that used the instrument in low-income, multiethnic settings. Also needs info on test-retest reliability.	Measure needs to be validated for people with asthma in diverse US samples.	Needs more studies on psychometric properties in diverse US samples.

(Continued)

TABLE III. *(Continued)*

	ABP	AIS-6	AQLQ	AQLQ-S	Mini-AQLQ	LWAQ	AQLQ-Marks	M-AQLQ-Marks	ASF	SGRQ	AQ-20
		intervention study samples were more than 90% white).									
Strengths and weaknesses	*Strengths:* Captures psychosocial areas of burden and distress not measured in most QOL instruments. Exclusively measures perception of asthma's impact on QOL. *Weaknesses:* Not validated in a US sample. Relatively new instrument; Limited data on use in research.	*Strengths:* Short, simple measure for clinical populations. Rigorous development. *Weaknesses:* Has not been widely used, particularly in diverse samples. Cannot derive a separate score for patient perception of asthma impact on QOL.	*Strengths:* Widely used and validated (in both long and short forms) for use in multiple countries. Adapted to create versions for use in pediatric asthma and rhinitis. *Weaknesses:* Substantial overlap with domains in newer measures of asthma control. Poor reliability of its smaller subscales. MCID has been questioned in the literature. Original AQLQ is more time-consuming and complex to administer than the standardized version.	*Strengths:* Widely used and validated for use in multiple countries. Has also been adapted to create versions for use in pediatric asthma and rhinitis. Quicker and easier to use than original AQLQ. *Weaknesses:* MCID has been questioned in the literature. Overrepresentation of symptoms and functional status in total score; inability to distinctly measure patient perception of impact of asthma on QOL.	*Strengths:* The Mini-AQLQ has good reliability, cross-sectional validity, responsiveness, and longitudinal validity (per Web site) and behaves similarly to the full version AQLQ-S. *Weaknesses:* Psychometric properties are not as strong as the full version. Some researchers have questioned the methodology used to define the MCID. Total score is somewhat overrepresented by symptom and activity domains.	*Strengths:* Captures many domains. 50% of items across 11 domains focus on emotional and social impact of asthma. Good psychometric properties overall. *Weaknesses:* At 68 items/15-20 minutes, it is the lengthiest of the QOL measures, which reduces its feasibility. No evidence that the 11 domains differentially predict outcomes. Lacking evidence for responsiveness in US samples.	*Strengths:* The scale appears to be relatively independent of subject characteristics. It has some cross-sectional relations to other measures. Its validity has been established against some markers of asthma severity. *Weaknesses:* Less reliable and responsive to change, as compared with M-AQLQ-Marks. It is more suitable for use in clinical trials than for use in clinical practice. Relative to AQLQ-Juniper, its use in clinical research settings is limited.	*Strengths:* The measure has greater reliability and responsiveness than the original AQLQ-Marks. 10/22 items appear to assess perceived impact of asthma on QOL. *Weaknesses:* Limited data on MCID. Has not been validated in US samples or other samples outside Australia. Modified version has not been widely used.	*Strengths:* The scale is short and was carefully developed. Subscale scores have been shown to have discriminant validity, and both concurrent and predictive validation is strong. *Weaknesses:* It is unclear whether the ASF is available, and it may have been replaced by the AIS-6. info is not available on stability over time or psychometrics in more diverse samples or specific subgroups. Cannot derive a reliable measure of patients' perception of asthma impact on QOL.	*Strengths:* The SGRQ has been widely used, and evaluations of the psychometric properties of many of the translated versions have been published. Psychometric testing has demonstrated its repeatability, reliability, and validity. Sensitivity has been demonstrated in clinical trials. *Weaknesses:* At 50 items, it is one of the longest asthma QOL measures. Scoring is complex: Provides indirect measure of impact of asthma on QOL.	*Strengths:* Very simple and brief (2-3 min) to administer, well-validated, and responsive. *Weaknesses:* Unclear how applicable it is to diverse US samples. MCID has not been established. Does not yield any specific subscale scores to distinguish patients' perception of impact of asthma on QOL.
No. of published English-language studies using tool since 2000 (ie, original empiric studies that actually used tool in a sample of asthmatic patients)	3 studies (reported in 4 different articles, plus 3-4 reviews)	2 studies (1 validation study, 1 intervention study)	29 studies (reported in 31 articles)	15 studies	8 studies	17 studies (reported in 21 articles)	10 studies	1 study (reported in 3 articles)	4 studies	32 studies (reported in 35 articles)	10 studies

(Continued)

TABLE III. *(Continued)*

	ABP	AIS-6	AQLQ	AQLQ-S	Mini-AQLQ	LWAQ	AQLQ-Marks	M-AQLQ-Marks	ASF	SGRQ	AQ-20
Applicability to different populations	Translated for use in Norway and Japan; developed in UK; unclear whether applicable to US.	NA	Has been successfully linguistically and culturally translated for use in other countries.	Has been successfully linguistically and culturally translated for use in other countries.	Has been successfully linguistically and culturally translated for use in other countries.	May lack lifestyle-specific items for specific populations. Has been translated for use in other countries.	Has been translated for use in other countries.	NA	Has been translated into Spanish and Chinese for US samples.	Has been successfully linguistically and culturally translated for use in other countries.	Unclear. At least 1 item (re: maintaining the garden) is less applicable to urban and low-SES populations. Has been translated for use in other countries.

ACQ, Asthma Control Questionnaire; *AOMS,* Asthma Outcomes Monitoring System; *AQLQ-S,* Asthma Quality of Life Questionnaire-Standardized; *ATAQ,* Asthma Therapy Assessment Questionnaire; *BMI,* body mass index; *ED,* emergency department; *FWA,* functioning with asthma; *HAD,* Hospital Anxiety and Depression Self-Assessment Score; *ICC,* intraclass correlation coefficient; *IRT,* item response theory; *ITG,* Integrated Therapeutics Group; *ITG-ASF,* Integrated Therapeutics Group–Asthma Short Form; *IVR,* interactive voice response; *LASS,* Lara Asthma Symptom Scale; *LWAQ,* Living With Asthma Questionnaire; *M-AQLQ-Marks,* Modified Asthma Quality of Life; *MCID,* minimal clinically important difference; *MRC,* Medical Research Council; *NA,* not available; *NAEPP,* National Asthma Education and Prevention Program; *PDA,* personal digital assistant; *PEF,* peak expiratory flow; *PIA,* psychosocial impact of asthma; *RV%,* relative validity percentage; *SABA,* short-acting β-agonist; *SEM,* standard error of measurement; *SIP,* Sickness Impact Profile; *VLA,* valued life activity.
*Total number of items does not equal items enumerated above because some items cover more than 1 domain.

TABLE IV. Summary of pediatric QOL instruments

	CHSA-C (child)	CHSA (parent)	PAQLQ (child)	PACQLQ (caregiver)	Pictorial PAQLQ (child)	PedsQL 3.0 Asthma Module (child)
Author/developer						
	American Academy of Pediatrics	American Academy of Pediatrics	E. F. Juniper	E. F. Juniper	R. S. Everhart and B. H. Fiese	
Domains covered						
Symptom frequency	7 items		10 items		10 items	11 items
Perceived functional limitations						
Participation in normal activities	6 items	5 items	5 items	4 items		
Tolerance of physical environment						
Social relations		6 items				3 items on communication problems
Mood and emotional well-being	12 items (feelings about asthma)	22 items	8 items	9 items	5 items	
Perceived risk/fear						3 items on worry
Health and longevity		15 items				
Financial well-being						

(Continued)

TABLE IV. *(Continued)*

	CHSA-C (child)	CHSA (parent)	PAQLQ (child)	PACQLQ (caregiver)	Pictorial PAQLQ (child)	PedsQL 3.0 Asthma Module (child)
Bother						11 items on treatment problems (trouble using inhaler, forgetting, medications "make me feel sick")
Total no. of items	25 items	48 items	23 items	13 items	15 items	28 items
Instrument characteristics						
Response format	Text answers are accompanied by visual cues in the form of graduated circles. For each question, the child looks at the card and responds by verbalizing his/her answer or pointing to corresponding circle.	5-point Likert scale, with higher scores indicating better QOL	7-point Likert-type scale (1 = "severe impairment" to 7 = "no impairment")	7-point Likert scale (1 = "severe impairment" to 7 = "no impairment")	Pictorial response format —allows the child to anchor his/her response decisions among 3 thermometers, which are empty, half-filled, and filled, to represent "none," "some," or "all of the time."	Ages 8-18 years: 5-point Likert scale; ages 5-7 years: 3-point scale
Intended use	Clinical research and practice	Clinical research and practice	Measurement of the functional problems (physical, emotional, and social) that are most troublesome to children with asthma	Measurement of the problems that are most troublesome to the parents (primary caregivers) of children with asthma	Measurement of asthma-specific QOL directly from young children.	Not reported
Target population	Children aged 7-16 years	Children aged 5-12 years (but used in ages 2-17)	Children aged 7-17 years	Parents of children aged 7-17 years	Children aged 5-7 years	Children with asthma aged 2-18 years
Time to complete	Average 9-10 minutes. Average completion time varies with age: 13 minutes at age 7 years; 7 minutes at age 13 years; children <10 years require greater response time.	20 minutes for telephone administration (less for self-administration)	10-15 minutes	3-5 minutes		Not reported. Note that this is 1 of many disease-specific modules that is part of the PedsQL general instrument.
Patient vs proxy report	Patient (child) report	Parent	Patient (child) report	Proxy	Patient (child) report	Parent proxy (for children aged 2-4, 5-7, 8-12, and 13-18 years) and children (aged 5-7, 8-12, and 13-18 years)
Method of administration	Interviewer-administered	Self-administered using paper and pencil	Interviewer- administered version recommended for use with children <11 years. Otherwise, can be self-completed.	Self-administered, paper and pencil or electronic version	Interviewer-administered; the child is asked to indicate his/her response anywhere on the line below the 3 thermometers.	Self-administered (for children aged 2-4 years, parents complete)
Recall period	2 weeks	2-, 4-, and 8-week versions	1 week	1 week	1 week	1 month
Reading level	Grade 3	Grade 6	NA	NA	NA	Not reported
Languages in addition to English	None	Spanish (for US)	>20	>20	None	Not reported
Cost to use	Free for use in noncommercial research or clinical practice applications.	Free for use in noncommercial research or clinical practice applications.	Free for use in noncommercial research or clinical practice applications. Contact E. Juniper for permission to use. Otherwise, there is a 1-time fee.	Free for use in noncommercial research or clinical practice applications. Contact E. Juniper for permission to use. Otherwise, there is a 1-time fee.	Still under development.	The license fee for using the PedsQL scales, modules, and translations varies according to the study type and financing. See http://www.pedsql.org/conditions.html

(Continued)

TABLE IV. *(Continued)*

	CHSA-C (child)	CHSA (parent)	PAQLQ (child)	PACQLQ (caregiver)	Pictorial PAQLQ (child)	PedsQL 3.0 Asthma Module (child)
Scoring method	Scores 0-100; higher scores = better outcomes. Does not mention if additional software is needed or if the instrument needs to be scored centrally. 3 subscales: physical health, activities, and emotional health.	All scale items require subjects to respond on 5-point scale. 5 subscales: physical health, activity (child), activity (family), emotional health (child), and emotional health (family).	Overall score is the mean of all 13 responses (scores range from 1-7). Individual domain scores (emotional function, activity limitations) are the means of the items in those domains.	Overall score is the mean of all 13 responses (scores range from 1-7). Individual domain scores (emotional function, activity limitations) are the means of the items in those domains.	Children are asked to rate their response to each item anywhere on a line below the 3 thermometers, and a scoring template is used to score responses on the line. The range of values is 1 (empty thermometer) to 7 (full thermometer). Subscale scores are calculated from the mean of responses for each subscale, and total QOL is calculated from the mean of all responses.	Items are reverse scored and transformed to a 0-100 scale, with higher scores indicating better QOL.
Psychometric testing						
Reliability	Internal consistency: Across different ages, the majority of reliability estimates for CHSA-C scales were ≥0.70. Range was 0.61 (for 8-year-olds completing physical health subscale) to 0.93 (14-year-olds, emotional health). Internal consistency tended to increase with child's age. Internal consistency ≥0.70 for all sex, race/ethnicity, and income groups.[98,99] Test-retest reliability: Correlation between forms ranged from 0.83 (physical health, child activities) to 0.89 (emotional health); ICC = 0.88. (physical health) −0.91 (child activities). Stratified by age, younger children were generally less reliable; lowest = 0.57, although most ages' reliability estimates were above 0.75. Reliability was strong for all sex, race/ethnicity, and income groups.[98,99]	Internal consistency: In addition to high-item-total correlations for the majority of items, Cronbach's α is very high for the total score (0.94) and moderately high for the various subscales: child physical health α = 0.89-0.92, child emotional health α = 0.87-0.91, child activity α = 0.81-0.89, family emotional health α = 0.65-0.90, family activity α = 0.79-0.85.[100] The subscales of the CHSA are moderately correlated with one another (r = 0.23-0.66).[101] Test-retest reliability: Correlation among forms was very high (0.81-0.86) for all subscales except child emotional health (0.62).[100]	Internal consistency: Cronbach's α = 0.92,[102] 0.86 for a pictorial version.[103] Paper and electronic forms are consistent with each other.[19] In Thailand sample, Cronbach's α = 0.83-0.97 across domains and assessments.[104] In Spanish sample, α also high: overall = 0.95, symptoms = 0.91, activities = 0.86, emotions = 0.89.[105] In Swedish sample, overall α = 0.92, symptoms = 0.86, activities = 0.79, emotions = 0.84.[106] Test-retest reliability: Test-retest conducted among patients with stable asthma (n = 37, stability measured using 3 methods); within-subject SD of change was 0.17 for the overall QOL score. Related to total variance, ICC = 0.95. Similar findings reported for the 3 domain scores.[107] Stability was acceptable for electronic version: overall ICC = 0.78, activity limitation = 0.66, symptoms = 0.76, emotional function = 0.80.[19] In Thailand sample, there was also good stability (ICC = 0.78-0.84 across domains).	Internal consistency: Cronbach's α for overall score = 0.92 in US sample.[19] In Swedish sample, α = 0.89 for the overall score, 0.90 for activities, and 0.87 for emotions.[108] Also, electronic versions have been developed.[109] Test-retest reliability: ICC = 0.84 among the parents who said their child's asthma was stable.[110] Stability was acceptable for electronic version: overall ICC = 0.85, activity limitation = 0.78, emotional function = 0.85.[19]	Internal consistency: Factor 1, Cronbach's α = 0.83, Factor 2, Cronbach's α = 0.71. Total QOL score, Cronbach's α = 0.86.[103]	In an American sample of children aged 8-12 years,[111] internal consistency reliability coefficients for each scale ranged from 0.58 (child self-report, treatment problems) to 0.91 (parent proxy report, asthma symptoms). In a sample of 252 "vulnerable children" in FQHCs,[112] asthma symptoms α was 0.78 for child self-report and 0.81 for parent proxy report. In a US sample of 70 black children with persistent asthma, α = 0.90.[113]

(Continued)

TABLE IV. *(Continued)*

	CHSA-C (child)	CHSA (parent)	PAQLQ (child)	PACQLQ (caregiver)	Pictorial PAQLQ (child)	PedsQL 3.0 Asthma Module (child)
Validity	Validity: Lower CHSA-C scores (indicating worse asthma QOL) on all 3 subscales were observed among children with more symptom days. Lower scores on all subscales also were observed among children whose parents reported higher medication use (SABA and nebulizer treatment). Higher CHSA-C scores on all subscales were observed among children whose parents described their health as very good-excellent. However, there was no consistent relationship between CHSA-C subscale scores and lung functioning (FEV_1).[98,100] Validity estimates by child sex, race/ethnicity, and income paralleled the overall sample.	Lower total CHSA scores were associated with more healthcare utilization, asthma symptom days, school absences, and caregiver distress.[114] Children with airway obstruction, measured by FEV_1 ratio, had lower total CHSA scores in 1 study,[115] but another study found that FEV_1 is not consistently correlated with CHSA.[114] With respect to subscales, physical health, family activity, child emotional health, and family emotional health (all but child activity) were associated with symptom severity. Child physical and emotional health were associated with medication use, but the other subscales were not.[100] CHSA physical health, child activity, family activity, and child emotional health were all correlated with number of wheezing episodes ($r = -0.16$ to 0.61, depending on the subscale and time point), number of asthma attacks ($r = -0.12$ to 0.50), symptom days ($r = -0.08$ to 0.45; -0.32 to 0.45 at strongest follow-up), and night wakings ($r = -0.06$ to 0.41; -0.32 to 0.45 at strongest follow-up). Physical health, child activity, and family activity (not emotional health) were associated with bronchodilator use, $r = -0.45$, -0.38, and -0.28, respectively, at 1-year follow-up.[114] While the results are not totally consistent, overall there is little evidence that the different subscales differentially predict various asthma outcomes.	Longitudinal validity was assessed against several measures: clinical change in asthma (lung function tests, SABA use), feeling thermometer, patients' global ratings of change, caregivers' perception. Cross-sectional concurrent validity measured against clinical change in asthma and feeling thermometer. Moderate associations for most, some mixed results, no correlation with FEV_1 % predicted Overall, PAQLQ had strong longitudinal and cross-sectional correlations with asthma indices and general QOL, across domains and age strata.[107] Total and all subscale scores negatively correlated with disease duration ($r = -0.28$ to 0.37), activity scale negatively correlated with asthma symptoms ($r = -0.26$). There were significant correlations between PAQLQ and various triggers: emotions $r = -0.41$, animal allergens $r = 0.18$, pollen allergens $r = 0.12$, physical activity $r = 0.30$, air pollution/irritants $r = -0.30$, infection $r = -0.16$.[117] Worse emotion domain scores were significantly related to worse asthma control, more days of missed school, and doctor visits for worsening asthma.[118] PAQLQ and PACQLQ were significantly intercorrelated ($r = 0.56$).[119] Also, evidence for convergent, discriminant, and predictive validity of pictorial version.[103] There is evidence for the PAQLQ's validity in several international samples. In a Dutch sample, all 3 PAQLQ	Validity was assessed against a separate generic caregiver burden of illness scale and several measures of child's asthma severity. Moderate to strong correlations were found between the PACQLQ and caregiver burden of illness.[110] Total score, emotional function, and activity limitation subscales all correlated with various measures of child's asthma severity (symptom-free days, etc). Total scores and emotion function scores also were associated with medication use and secondhand smoke exposure—while activity limitation was only associated with symptom variables.[133] Total scores also associated with parent-reported family burden and child-reported QOL.[134] PAQLQ and PACQLQ were significantly correlated ($r = 0.56$).[119] In a French sample, parent QOL was significantly associated with the child's emotional and academic self-esteem, psychological symptoms, and QOL, but was not associated with child asthma severity.[131] In an Iranian sample, parent QOL was associated with child asthma severity.[132] In an Israeli sample, parent total and domain scores were correlated with child scores, but not child FEV_1 or asthma severity.[109] In a Dutch sample, PACQLQ scores were lower among caregivers of children with asthma vs controls, but children had lower scores than did caregivers in the activity domain.[135] In a Swedish	*Convergent validity:* Symptom subscale scores significantly correlated with total scores on the PACQLQ ($M = 5.34$, $SD = 1.49$; $r = 0.23$, $P < 0.05$). Scores on emotional subscale correlated with total PACQLQ scores ($r = 0.23$, $P < 0.05$). Scores on symptoms subscale related to FEV_1 scores ($M = 1.48$, $SD = 0.51$; $r = 0.22$, $P < 0.05$). *Discriminant validity:* Verbal ability for the 5-year-olds (based on WPPSI-Revised vocabulary subtest) was not significantly correlated with scores on either subscale. Scores on the emotional subscale were not correlated with verbal ability (WISC) for 6- to 7-year-olds, but scores on the symptoms subscale were correlated with verbal ability on the WISC for this age group ($r = 0.29$, $P < .05$). There is no info on whether each of the subscale scores provide unique info (ie, on what is the discriminant validity of the subscale scores relative to one another). *Predictive validity:* For the children followed longitudinally until 8 years of age ($n = 48$), scores on the symptoms subscale demonstrated predictive validity with the symptoms subscale of the PAQLQ ($M = 5.56$, $SD = 1.25$; $r = 0.51$, $P < 0.01$), after controlling for child's age at the initial visit. Scores on the emotional subscale demonstrated predictive validity with the emotions subscale of the PAQLQ ($M = 5.65$, $SD = 1.35$; $r = 0.41$, $P < 0.01$).	Construct validity was based on intercorrelations among the PedsQL 3.0 generic core total scale score, as well as a modified multitrait-multimethod matrix. Convergent validity was tested by examining the intercorrelations between the PedsQL 3.0 Asthma Module scales and the PAQLQ.[111] Seid (2010)[112] noted intercorrelation between generic core scales and Asthma Module asthma symptoms scale score. Greenley (2008)[113] examined intercorrelations of the subscales with one another and with total score to assess convergent validity. The PedsQL 3.0 Asthma Module total score was highly correlated with all subscale scores (r values ranged from 0.72 to 0.89). There was also correlation between the child report and the parent proxy report measure for asthma symptoms (but not for treatment problems, worry, or communication).

(Continued)

TABLE IV. *(Continued)*

CHSA-C (child)	CHSA (parent)	PAQLQ (child)	PACQLQ (caregiver)	Pictorial PAQLQ (child)	PedsQL 3.0 Asthma Module (child)
	Worse CHSA physical health status was associated with socioeconomic factors: lower family income, increasing family size, and living in a single-adult household. Even after adjusting for these factors, black children's CHSA physical health scores were significantly lower than white children's (average of 6 points lower on a 1-100 scale).[116]	domains correlated with SABA use (r = 0.30-0.34); only activity domain correlated with FEV_1 (r = 0.26) and PEF (r = 0.21).[120] For all domains, QOL was lower among children with asthma vs controls, and those with both asthma and excessive body weight.[121] In the Italian sample, PAQLQ significantly correlated with clinical and functional indices, including asthma control and severity.[122] In the Polish sample, PAQLQ total score did not differ among children with different asthma severity levels, but there was a significant correlation between PAQLQ and PEF variability (r = 0.35).[123] In the Israeli sample, total and domain scores were correlated with parent scores, but not FEV_1 or asthma severity.[109] In Spanish samples, significant moderate correlations between the PAQLQ scores and the Asthma Control Score (0.53-0.67), the General Health Perception (0.34-0.55), and the % PEF (0.44-0.55).[105] PAQLQ total score also was associated with asthma severity, immunotherapy, geographic location of residence, and season.[124] In a Thai sample, correlations between PAQLQ domains, asthma diary, PEF, and SABA use were found to be moderate (r = 0.31-0.69); there was no significant correlation with FEV_1% (r = 0.01-0.03).[104] In a German sample, total and subdomain scores all decreased as severity increased.[125] In a Swiss sample, PAQLQ correlated with the German version of Adolescent Asthma Quality of Life Questionnaire (r = 0.86),	sample, overall and both domain scores were all associated with asthma severity from medical records, symptoms rated by caregiver, and child QOL.[108] Rationale and construct validity: Items were generated from interviews of parents of children with asthma, literature review, and discussion with health professionals. Items caregivers rated as most bothersome were included in the measure.[110] It is unclear whether the 2-dimension structure has validity: 1 factor analysis study found a 2-factor solution, but these 2 factors did not map onto Juniper's suggested domains.[134]		

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TABLE IV. *(Continued)*

	CHSA-C (child)	CHSA (parent)	PAQLQ (child)	PACQLQ (caregiver)	Pictorial PAQLQ (child)	PedsQL 3.0 Asthma Module (child)
			patient-rated symptom severity ($r = 0.76$), coughing, wheezing, shortness of breath, and sleep ($r = -0.42$ to 0.50).[126] There is also evidence for validity from samples in Sweden, Jordan, Australia, Brazil, Turkey, France, and Iran.[107,127-132]			
Responsiveness (sensitivity to change)	NA	4 studies found evidence of within-subject changes in the CHSA over time.[114,136-139] All 5 individual subscales have demonstrated some responsiveness. Some individual studies report changes in 1 subscale but not another, but there is no clear pattern of evidence suggesting that some subscales are more responsive overall. Between subjects, there is evidence that as severity increased, QOL measured by the CHSA decreased, and that the CHSA can discriminate between children with and without airway obstruction.	Responsiveness measured among those whose asthma had changed over a 4-week period, either due to treatment or natural fluctuations (n = 32). Mean change among this group in overall QOL during a 4-week period was 0.98 (SD = 0.88); similar changes were reported for subdomain scores. Thus the PAQLQ was able to detect changes and to differentiate patients whose health status changed from those who remained stable. Other US samples were similarly able to detect changes over time and in response to treatment.[140,141] There was some evidence of change in PAQLQ over time and/or in response to treatment in Brazilian, Chilean, Italian, Polish, Portuguese, Spanish, Swedish, Thai, Turkish, and multicountry international samples.	Able to detect within-subject changes in QOL over time and to differentiate between scores (overall, both domains) of stable caregivers and those whose HRQL changed between assessments ($P = .0003$).[110] US and international studies were able to detect improvements in PACQLQ in response to treatment.[108,119,142,143] There is also evidence that changes in caretaker's QOL are associated with changes in child's asthma symptoms.[133,144]	Group differences were found according to race; minority children reported significantly poorer scores on the symptoms subscale and the emotions subscale compared with white children ($P < .05$). Group differences also were found by recruitment site, with children recruited from the teaching hospital reporting significantly worse QOL than children recruited from the pulmonary clinic or private pediatric clinics.	Seid (2010)[112] noted that within-subject change from baseline to 3-month follow-up improved for those also classified as clinically improved by asthma symptom frequency. Varni (2004)[111] reported responsiveness analysis, which was limited to 10 children on symptom scale only.
MCID	NA	MCIDs have not been established for 4 of the 5 CHSA scales. However, preliminary studies of physical health scale scores estimate an MCID with a range from 0.83 (SD = 0.39) to 1.24 (SD = 1.32) (L. Asmussen, written communication, Oct 2003, as cited in Lozano et al, 2004[137]).	MCID was measured by assessing score differences against a global rating of change provided by the child (responses were scored on a 15-point scale; criterion was a 2- to 3-point change. MCID for overall QOL = 0.42; symptoms domain = 0.54; activity domain = 0.70; emotional function domain = 0.28. However, the 1 recent study that actually described results in terms of MCID used 0.50.[145]	MCID measured against a global rating of change (15-point, 1-item scale) of the child's asthma provided by the parent. MCID for overall caregiver QOL was 0.50, with similar values for the emotional function domain (0.64) and the activity limitation domain (0.67).	NA	Not reported

(Continued)

TABLE IV. *(Continued)*

	CHSA-C (child)	CHSA (parent)	PAQLQ (child)	PACQLQ (caregiver)	Pictorial PAQLQ (child)	PedsQL 3.0 Asthma Module (child)
Sample size(s) tested	414 parent/child pairs	Originally validated in 3 different studies, involving 276 subjects; later used in samples ranging from 45 to 13878	Originally validated in sample of 52 children (aged 7-17 years)[146]; recent studies with n ranging from 19 to 1758	Originally validated in parents of 52 Canadian children; recent studies with n ranging from 32 to 621	Initial development and testing of this measure with 101 children with mild to severe asthma; 48 children followed longitudinally	Children with asthma aged 5-16.4 years (n = 404) and parents of children aged 2-16.4 years (n = 526), with 529 families overall.[111] Children in FQHCs (n = 252); age range 3-14 years; mean age, 7.8 years; varying degrees of asthma severity (27% mild; 41% moderate; 32% severe).[112] US children participating in a randomized controlled trial for black children with persistent asthma (n = 70); age range 9-17 years; mean age, 12.2 years.[113] Varni's sample size appears to be a total of 165 participants who completed the Asthma Module, drawn from several sources: a study of families who were newly enrolled in an SCHIP (n = 364), children with asthma who were newly enrolled in a treatment research study at the University of Kansas Medical Center (n = 86), and children with asthma who attended a summer camp sponsored by the American Lung Association (n = 79).[111]
Sample characteristics —income/SES, race/ethnicity, country	Children and parent pairs from the cities and surrounding suburbs from Chicago, Ill, and Cincinnati, Ohio	See Table III of Asmussen (1999) paper.[100] Several studies utilized diverse samples, including predominantly low-income/SES individuals and/or predominantly black or Hispanic samples. Some studies using the CHSA had predominantly male samples.	Original validation study: Income/SES and race/ethnicity not reported; country, Canada; age, 7-17 years (mean = 12.0); sex, 22 females and 30 males. Recent studies have included racially and socioeconomically diverse US samples, as well as samples from several other countries.	Original validation study: Income/SES and race/ethnicity not reported; country, Canada; age, 7-12 years (mean = 12.0); sex, 22 females and 30 males. Recent studies have included racially and socioeconomically diverse US samples and samples from several other countries.	More than half the children were boys (64%); 56% were white; 25% were black; 3% Hispanic; 1% Native American; and 15% mixed race.	Tested in a sample of 252 "vulnerable children" in FQHCs; 83% Hispanic.[112] Tested with children participating in a randomized controlled trial for black children with persistent asthma (n = 70), living in inner-city neighborhoods with income below the poverty line. Age range was 9-17 years; mean age, 12.2 years.[113]
Diversity in psychometric evaluation (different populations, methods of administration, age groups, etc)	Subjects were 7-16 years old (average = 11.5 years), 59% male, 45% black, 11% Hispanic, and >40% reported annual household income <$30K.	Original validation sample included large numbers of ethnic minorities (black, Hispanic) and low education/low income individuals. More recent validation studies also used ethnically and socioeconomically diverse samples.	Psychometric data are available from diverse US samples and international samples (eg, Spain, Sweden, Thailand), which incorporate various languages and age, socioeconomic, and race/ethnic groups.	Psychometric data are available from diverse US samples and international samples (eg, Sweden).	NA	Tested with 301 boys and 227 girls. Age range was 2-16.4 years; average age 8.8 years. Tested with primarily white non-Hispanic and Hispanic patients.

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TABLE IV. *(Continued)*

	CHSA-C (child)	CHSA (parent)	PAQLQ (child)	PACQLQ (caregiver)	Pictorial PAQLQ (child)	PedsQL 3.0 Asthma Module (child)
Instrument summary						
Additional info needed	Need more info about population norms.	Need more info on discriminant validity of subscales.	Need more info on discriminant validity of subscales.	Need more info on discriminant validity of subscales.	This is a new adaptation of the PAQLQ. Need further testing to confirm the proposed factor structure and provide validation.	See above. Varni (2004)[111] noted, "Until further testing is conducted, the child self-report scale that did not achieve the standard 0.70 should be used only for descriptive or exploratory analyses."
Strengths and weaknesses	*Strengths:* Little burden, evidence of reliability and validity in an ethnically and socioeconomically diverse sample. Validation in children aged 7-16 years. *Weaknesses:* Longer administration time and decreased reliability and validity in children younger than 10 years. Overlap with measures of asthma control. Newer measure (2008); limited data on use.	*Strengths:* Can be reliably used even when reporting on younger children. Evidence of reliability and validity in ethnically and socioeconomically diverse samples. Can be used in combination with child-report version. *Weaknesses:* At 48 items, 20 minutes, longer than other commonly used asthma QOL measures. Perceived impact of asthma on QOL is inferred from activity and emotional subscales.	*Strengths:* The instrument has been used in a number of pediatric studies in the US and abroad and is available in multiple languages. Published original studies show strong reliability, validity, and responsiveness in diverse US and international samples, although original validation was a small sample. *Weaknesses:* At present, lacks evidence for discriminant validity of subscales. Predominance of items are related to health status and functional status.	*Strengths:* Companion survey for children (PAQLQ) has been fairly widely used in pediatric asthma studies. Measure has good reliability, validity, and responsiveness, and PACQLQ has been used in diverse samples. It is brief (13 items, 3-5 min). *Weaknesses:* At present, lacks evidence for discriminant validity of subscales. Does not measure impact of children's asthma on parents except in terms of the emotional domain.	*Strengths*: The Pictorial PAQLQ holds promise as a new measure for direct reporting of QOL by young children. This is particularly important, since info from young children can provide info that is distinct from info obtained from their caregivers, and few measures currently are available for this age group. Development of the instrument was based on the well-established PAQLQ, with specific attention to the cognitive abilities and developmental status of young children. Initial testing suggests adequate psychometric properties; provides preliminary evidence of validity. *Weaknesses:* This measure is newly developed, and further evaluation is needed. It relies on a pictorial format, and therefore would not be applicable to telephone surveys.	*Strengths:* Although the PedsQL core instrument is well defined, the psychometric properties of the asthma module instrument are emerging. *Weaknesses:* Limited published data on population norms, data regarding burden, and data regarding MCID.
No. of published English-language studies using tool since 2000 (ie, original empiric studies that actually used tool in a sample of asthmatic patients)	1 study (reported in 2 articles)	12 studies (reported in 14 articles)	44 studies, including 14 clinical trials (reported in 46 articles)	19 studies, including 6 clinical trials (reported in 20 articles)	Not determined	Not determined
Applicability to different populations	Applicable to minority and low-income populations in US; not tested in other countries or languages.	Applicable to minority and low-income populations in US, including Spanish-speaking US residents; not tested in other countries.	Applicable to minority and low-income populations in the US; also tested in several other countries; available in many different languages.	Applicable to minority and low-income populations in the US; also tested in several other countries; available in many different languages.		Applicable to wide age range; has been used in different US racial/ethnic groups.

CHSA, Child Health Survey for Asthma; *CHSA-C,* Child Health Survey for Asthma-Child Version; *FQHC,* federally qualified health center; *HRQL,* health-related quality of life; *ICC,* intraclass correlation coefficient; *MCID,* minimal clinically important difference; *NA,* not available; *PACQLQ,* Pediatric Asthma Caregiver Quality of Life Questionnaire; *PAQLQ,* Pediatric Asthma Quality of Life Questionnaire; *PEF,* peak expiratory flow; *SABA,* short-acting β-agonist; *SCHIP,* State Children's Health Insurance Program; *6MWD,* 6-minute walking distance; *WPPSI,* Wechsler Preschool and Primary Scale of Intelligence.

asthma management—that the asthma module does not directly assess the child's perspective on how his or her life is affected by asthma or how much asthma bothers him or her. There are limited published data on population norms, respondent burden, and the minimally important difference. Except for cases of unfunded academic research, there is a fee for using this instrument.

Recommendation. The subcommittee recommends classifying the PedsQL 3.0 Asthma Module as a supplementary instrument for use in clinical research.

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Asthma Symptom Utility Index: Reliability, validity, responsiveness, and the minimal important difference in adult asthmatic patients

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Background: The evaluation of asthma symptoms is a core outcome measure in asthma clinical research. The Asthma Symptom Utility Index (ASUI) was developed to assess the frequency and severity of asthma symptoms. The psychometric properties of the ASUI are not well characterized, and a minimal important difference (MID) is not established.
Objectives: We assessed the reliability, validity, and responsiveness to change of the ASUI in a population of adult asthmatic patients. We also sought to determine the MID for the ASUI.
Methods: Adult asthmatic patients (n = 1648) from 2 previously completed multicenter randomized trials were included. Demographic information, spirometric results, ASUI scores, and other asthma questionnaire scores were obtained at baseline and during follow-up visits. Participants also kept a daily asthma diary.
Results: The internal consistency reliability of the ASUI was 0.74 (Cronbach α). Test-retest reliability was 0.76 (intraclass correlation). Construct validity was demonstrated by significant correlations between ASUI scores and Asthma Control Questionnaire scores (Spearman correlation $r = -0.79$; 95% CI, −0.85 to −0.75; $P < .001$) and Mini Asthma Quality of Life Questionnaire scores ($r = 0.59$; 95% CI, 0.51-0.61; $P < .001$). Responsiveness to change was demonstrated, with significant differences between mean changes in ASUI scores across groups of participants differing by 10% in percent predicted FEV_1 ($P < .001$) and by 0.5 points in Asthma Control Questionnaire scores ($P < .001$). Anchor-based and statistical methods support an MID for the ASUI of 0.09 points.
Conclusions: The ASUI is reliable, valid, and responsive to changes in asthma control over time. The MID of the ASUI (range of scores, 0-1) is 0.09. (J Allergy Clin Immunol 2012;130:1078-84.)

Key words: *Asthma Symptom Utility Index, reliability, validity, responsiveness, minimal important difference*

Asthma is a chronic disease associated with substantial morbidity.[1] Recent asthma guidelines highlight the need to achieve and maintain good disease control.[1,2] Well-validated questionnaires, such as the Asthma Control Questionnaire (ACQ)[3] and the Asthma Control Test,[4] are often used to assess asthma control in research and clinical practice. Asthma-specific quality-of-life questionnaires, such as the mini Asthma Quality of Life Questionnaire (Mini AQLQ)[5] and the Marks Asthma Quality of Life Questionnaire (AQLQ-Marks),[6] gauge the effect of asthma on the patient's functioning and well-being. The evaluation of asthma symptoms is a recommended core outcome measure in asthma clinical research, yet there is currently no widely accepted instrument for the standardized measurement of asthma symptoms.[7]

A recent National Institutes of Health working group found the Asthma Symptom Utility Index (ASUI) to be promising but not adequately validated.[7] The ASUI was developed in 1998 by Revicki et al[8] to measure the degree of asthma symptoms and their effect on patients. Some items on the ASUI are similar to those on questionnaires that assess asthma control and asthma-related quality of life.[3,5,9,10] However, composite scores obtained from these questionnaires allocate equal weight to each item, even though the effect of different symptoms on patients might vary. The ASUI is unique insofar as it is a weighted scale and thus particularly valuable in cost-utility analyses.[8] It is increasingly being used in asthma clinical research.[11,12] The initial study by Revicki et al[8] showed that the ASUI had good reproducibility (intraclass correlation = 0.74), good construct validity (Pearson correlation coefficient with the AQLQ = 0.77), and good discriminant validity. Nonetheless, a comprehensive evaluation of the psychometric

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Abbreviations used
ACQ: Asthma Control Questionnaire
AQLQ: Asthma Quality of Life Questionnaire
ASUI: Asthma Symptom Utility Index
EPAC: Episodes of poor asthma control
MID: Minimal important difference
PEFR: Peak expiratory flow rate
SARA: Study of Acid Reflux and Asthma
SIIVA: Safety of Inactivated Influenza Vaccine in Asthma

properties of the ASUI is lacking. In addition, a minimal important difference (MID) for the ASUI has not been established. Our objectives were to assess the reliability, validity, and responsiveness to change of the ASUI in a population of adult asthmatic patients participating in 2 multicenter randomized trials. We also sought to determine the MID for the ASUI.

METHODS

ASUI

The ASUI is a 10-item self-administered questionnaire with 4 questions on asthma symptoms (cough, wheeze, shortness of breath, and awakening at night) and 1 question about the side effects of asthma medications. For each symptom, there are 2 dimensions: frequency and severity. The questionnaire is based on a 2-week patient recall of symptoms and is scored by using a previously derived multiattribute utility function.[8] The weighting scheme of the ASUI was developed by first constructing health states with single or multiple asthma symptoms at different frequencies and severities.[8] Next, the participants were asked to attribute a relative value to various health states by using a visual analog scale and standard gamble methods.[8] Finally, these data were used to derive a multiattribute utility function for scoring individual symptoms.[8] The summary score is a continuous scale from 0 to 1, with lower scores indicating worse asthma symptoms.[8] Details on the development of the ASUI have been previously published.[8]

Data collection

Patients. Data from 1648 adult asthmatic participants (≥18 years) enrolled in 2 completed clinical trials conducted by the American Lung Association Asthma Clinical Research Centers were included in this analysis.[11,13] The Safety of Inactivated Influenza Vaccine in Asthma (SIIVA) trial was conducted between September 15 and November 30, 2000, and showed that the inactivated trivalent split-virus influenza vaccine was safe in adults and children with asthma.[13] The Study of Acid Reflux and Asthma (SARA) trial was conducted between October 2004 and May 2008.[11] It showed that proton pump inhibitors did not improve asthma control in adults whose asthma was not well controlled on inhaled corticosteroids.[11]

Procedures. The protocols for both studies were approved by institutional review boards in each of the participating centers, and informed consent was obtained from each participant. The SARA trial was registered at ClinicalTrials.gov (NCT00069823); the SIIVA trial was conducted before National Institutes of Health registration requirements were instituted. In the SIIVA trial baseline demographic data and ASUI scores were obtained for all participants (n = 1236). Baseline spirometric results were obtained in a subset of participants (n = 704). After administration of either vaccine or placebo, participants were followed for 14 days, during which they kept a daily asthma diary with information on asthma-related symptoms, peak expiratory flow rate (PEFR), health care use, and medication use. After crossover, there was another 14-day follow-up period.[13] In the SARA trial (n = 412) baseline demographic data, spirometric results, ASUI scores, ACQ scores, and Mini AQLQ scores were obtained. Patients were then randomized to either 40 mg of esomeprazole twice daily or placebo in addition to their inhaled corticosteroid regimen for a total of 24 weeks. During follow-up clinic visits that occurred every 4 weeks, ASUI, ACQ, and Mini AQLQ scores were obtained. Patients also kept an asthma diary that was returned during each clinic visit.[11]

Assessments

Reliability. The Cronbach α coefficient was calculated by using baseline ASUI data from both the SIIVA and SARA trials to evaluate the internal consistency reliability. The Cronbach α coefficient measures the degree to which the items on the questionnaire measure the same unidirectional construct. Test-retest reliability was assessed by calculating the intraclass correlation coefficient between the baseline ASUI score and the ASUI score at the next follow-up visit (4 weeks apart) using data from participants in the SARA trial with stable asthma. Stable asthma was defined by the absence of an episode of poor asthma control (EPAC)[11] and no clinically significant change in the ACQ scores[3] and Mini AQLQ scores[5] (change <0.5 points). An EPAC was defined by the occurrence of at least 1 of the following events: an increase in rescue medication use for asthma symptoms by 4 or more inhalations per day over baseline, the occurrence of an unscheduled contact with a health care provider for asthma, use of systemic corticosteroids for asthma, or a decrease of 30% or greater in morning PEFR on 2 consecutive days compared with the patient's best PEFR during the run-in period.[11]

Construct validity. Construct validity of the ASUI was assessed with data from the SARA trial by computing Spearman correlations between baseline ASUI scores and (1) baseline ACQ[3] scores and (2) baseline Mini AQLQ[5] scores.

Known-groups validity. Known-groups validity was assessed by using data from the SIIVA trial, comparing the mean baseline ASUI score across 3 categories of baseline percent predicted prebronchodilator FEV_1: (1) less than 60%, (2) 60% to 79%, or (3) 80% or greater. The mean baseline ASUI score was also compared across a 4-point scale of ascending asthma severity among SIIVA participants based on asthma medication use at baseline (1, intermittent; 2, mild; 3, moderate; and 4, severe).[14] Asthma severity was assessed according to an approximate Global Initiative for Asthma medication classification.[14] Data on other methodologies for assessing asthma severity, such as the National Asthma Education and Prevention Program and Global Initiative for Asthma classifications, were not available for this *post hoc* analysis. Previous studies have shown that current asthma medication use complements other classifications of asthma severity.[15,16] One-way ANOVA was then used to test the significance of differences in mean ASUI scores across groups of patients who differed by percent predicted FEV_1 and asthma severity categories.

Predictive validity. By using data from the SIIVA trial, predictive validity was assessed by comparing the frequency of EPACs and asthma exacerbations over the next 2 weeks by quartiles of baseline ASUI scores. An asthma exacerbation was defined by new use of systemic corticosteroids or an unscheduled contact with a health care provider. The ASUI was classified by quartiles because on exploratory data analysis, baseline ASUI scores had a skewed distribution, such that a majority of patients had very high scores and fewer patients had low scores. By using the highest ASUI quartile as the reference, the relative risk for each quartile of baseline ASUI scores was then calculated.

Responsiveness. Data from the SARA trial were used to determine the responsiveness to change in ASUI score. For each participant, there were 7 clinic visits, each separated by 4-week intervals from randomization to the end of the study. During each clinic visit, ASUI, ACQ,[3] and Mini AQLQ[5] scores were obtained. All participants were instructed to keep a daily asthma diary that was returned to the clinic during subsequent visits. Linear regression with robust variance estimates and an exchangeable correlation structure was used to compare mean changes in ASUI scores across groups of participants who differed by more than 10% in percent predicted FEV_1 and by greater than 0.5 points in ACQ scores while adjusting for visit period.[17] The participant groups for each measure were derived as follows:

1. *Percent predicted FEV_1*: Previous studies have used 10% as the cutoff for significant change in percent predicted FEV_1.[9,10,18] In the

population with chronic obstructive pulmonary disease, the MID of percent predicted FEV_1 is approximately 10%.[19] The change in percent predicted FEV_1 was derived by subtracting baseline percent predicted FEV_1 from follow-up percent predicted FEV_1 and dividing by the baseline percent predicted value. Participants were categorized as better if the increase in percent predicted FEV_1 was greater than or equal to 10%. They were categorized as worse if percent predicted FEV_1 decreased by greater than or equal to 10%. If the change was less than 10% in either direction, they were categorized as unchanged. The mean changes in ASUI scores were then compared among the 3 groups.

2. *ACQ scores*: The MID for the ACQ score is 0.5 points.[3] Participants were categorized as better if the decrease in ACQ score was greater than or equal to 0.5. They were categorized as worse if the increase in ACQ score was greater than or equal to 0.5, and they were categorized as the same or unchanged if the change was between −0.5 and +0.5 points. The mean changes in ASUI scores were then compared among the 3 groups: better, same, or worse.

MID. The MID is the smallest difference in score of an instrument that represents a clinically noticeable change.[20] In this study anchor- and distribution-based methods were used to determine the MID of the ASUI score.[5,18,20]

Anchor-based analysis. Two groups of change in percent predicted FEV_1 (<10% vs ≥10% improvement from baseline) and 7 groups of changes in ACQ scores from baseline ($\Delta ACQ \geq -1.5$, $-1.0 \leq \Delta ACQ < -1.5$, $-0.5 \leq \Delta ACQ < -1.0$, $+0.5 > \Delta ACQ < -0.5$ [no change], $+1.0 > \Delta ACQ \geq +0.5$, $+1.5 > \Delta ACQ \geq +1.0$, $\Delta ACQ \geq +1.5$) were used as "anchors" to evaluate meaningful differences in ASUI scores. One-way ANOVA was used to compare mean changes in ASUI scores across the groups in each case. The occurrence of an EPAC, as well as individual EPAC components, also served as anchors. The mean difference in ASUI scores between visits with an EPAC in the prior period and those without an EPAC were calculated by using repeated-measures ANOVA.

Distribution-based analysis. The SDs of the baseline ASUI scores for each study sample were calculated, and ½ SD was used as an estimate of the MID.[20] The SEM of the baseline ASUI scores for each sample was also computed as follows: $SEM = SD_{ASUI} \times \sqrt{(1 - reliability_{ASUI})}$.[18,20]

For the SIIVA sample, the Cronbach α coefficient was used to estimate the reliability coefficient of the ASUI, and for the SARA sample, the test-retest reliability coefficient was used. By convention, 1 SEM of baseline ASUI score is a good estimate of the MID.[18,20]

RESULTS

Study population

Data from 1236 study participants aged 18 years and older from the SIIVA trial were included. The mean age of these asthmatic patients was 42 years (SD, 12 years). A majority of them were female (75%) and white (67%). Data from 412 participants in the SARA trial were also included. The mean age of asthmatic patients in the SARA trial was 41 years (SD, 13 years). The majority were female (68%), 50% were white, and 38% were black. A summary of the baseline characteristics of the study participants from the SIIVA and SARA trials is presented in Table I.[21]

Reliability

The internal consistency reliability (Cronbach α) was 0.74 (n = 1223) in the SIIVA sample and 0.71 (n = 412) in the SARA sample. Test-retest reliability (intraclass correlation coefficient) among the 55 participants in the SARA trial with stable asthma over a 4-week period was 0.76.

TABLE I. Patients' characteristics at baseline

Characteristic	SIIVA trial (n = 1236)	SARA trial (n = 412)
Age, y (SD)	42 (12)	41 (13)
Female sex (%)	923 (75)	279 (68)
Race or ethnic group, no. (%)		
White	828 (67)	205 (50)
Black	281 (23)	157 (38)
Hispanic	79 (6)	41 (10)
Other	44 (4)	9 (2)
Asthma questionnaire scores, mean (SD)		
ASUI↑ (0-1)	0.82 (0.18)	0.76 (0.16)
ACQ↓ (0-7)	NA	1.7 (0.9)
Mini AQLQ↑ (1-7)	NA	4.7 (1.2)
Pulmonary function, mean (SD)*	SIIVA (n = 704)	SARA (n = 412)
Prebronchodilator FEV_1 (L)	2.6 (0.9)	2.4 (0.7)
Prebronchodilator FEV_1 (% predicted)	83.4 (21)	76.7 (15)

ASUI scores range from 0 to 1, with higher scores indicating less severe asthma symptoms. ACQ scores range from 0 to 7, with lower scores indicating better asthma control and 0.5 being the minimal clinically important difference. Mini AQLQ scores range from 1 to 7, with higher scores indicating better quality of life and 0.5 as the minimal clinically important difference. FEV_1 and the predicted values are from Hankinson et al.[21]

*Pulmonary function results were available for 704 (57%) SIIVA participants.

TABLE II. Known-groups validity tests on mean ASUI scores at baseline (SIIVA trial)

	No. of participants	Mean (SD) ASUI score	F statistic/*P* value
Percent predicted FEV_1			
<60%	97	0.76 (0.18)	
60% to 79%	188	0.81 (0.17)	
≥80%	405	0.85 (0.15)	12.5/<.0001
Asthma severity based on baseline medication use			
Intermittent	332	0.85 (0.14)	
Mild	453	0.83 (0.16)	
Moderate	298	0.80 (0.19)	
Severe	137	0.71 (0.20)	25.4/<.0001

FEV_1 and predicted values are from Hankinson et al.[21]

Construct validity

Statistically significant Spearman correlations were observed between baseline ASUI scores and baseline ACQ ($r = -0.79$; 95% CI, −0.85 to −0.75; $P < .001$) and baseline Mini AQLQ ($r = 0.59$; 95% CI, 0.51-0.61; $P < .001$) scores.

Known-groups validity

The difference in mean ASUI scores between patients with poor baseline lung function (percent predicted FEV_1 <60%) and those with good baseline lung function (percent predicted FEV_1 ≥80%) was statistically significant (0.76 vs 0.85, $P < .0001$, Table II). There was a positive linear relationship between the mean ASUI score and category of percent predicted FEV_1 (Fig 1). The difference in mean ASUI scores between patients with severe asthma and those with intermittent asthma was statistically significant (0.71 vs 0.85, $P < .0001$, Table II). There was a negative linear relationship between mean ASUI scores and asthma severity based on asthma medication use at baseline (Fig 2).

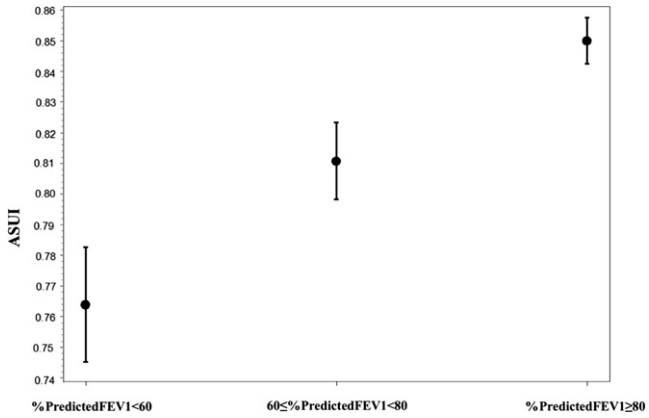

FIG 1. Mean ASUI scores with SEs by category of percent predicted FEV_1.

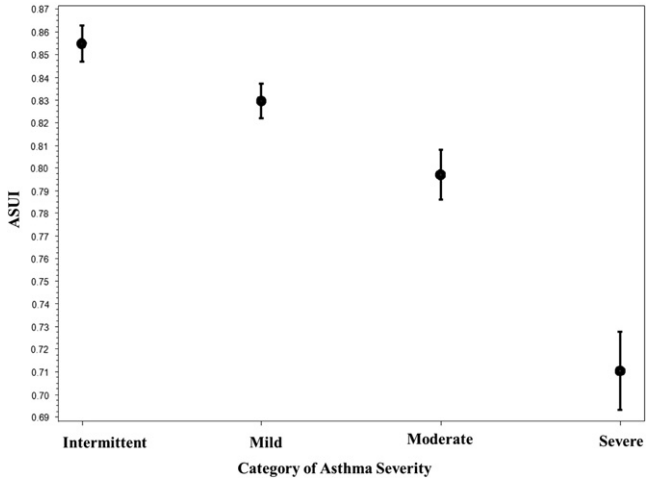

FIG 2. Mean ASUI scores with SEs by category of asthma severity.

Predictive validity

The frequency of EPACs ranged from 13% in the highest quartile of ASUI scores to 39% in the lowest quartile. Compared with patients in the highest quartile of baseline ASUI scores (score >0.95), SIIVA participants with a baseline ASUI score of 0.73 or less (lowest quartile) were 40% more likely to experience an EPAC over the next 2 weeks. There was a dose-response relationship with increasing likelihood of an EPAC by decreasing quartile of baseline ASUI scores (Table III). The overall frequency of asthma exacerbations, as defined by new or increased oral corticosteroid use or an unscheduled health care contact for asthma, was low (4% to 11%) across all 4 groups. Participants in the lowest quartile were 8% more likely to experience an exacerbation compared with those in the highest quartile (Table III).

Responsiveness

The ASUI demonstrated good responsiveness to change. As hypothesized, ASUI scores improved significantly among participants whose percent predicted FEV_1 improved by greater than or equal to 10% compared with those with no change in percent predicted FEV_1 (Table IV). Likewise, there was a significant change in ASUI scores (in the hypothesized direction) when ACQ scores changed by more than the MID of 0.5 points compared with when the ACQ scores were unchanged (Table IV). After adjusting for visit period, there was a statistically significant difference in mean change in ASUI scores between visits with an EPAC in the prior period and those without an EPAC ($P < .0001$, Table V). Similar significant differences were seen for all 4 EPAC components (Table V).

MID

Anchor-based results. The absolute mean change in ASUI score corresponding to a small change in ACQ score ($-0.5 \leq \Delta ACQ < -1.0$ or $+1.0 < \Delta ACQ \geq +0.5$) was 0.09 (Table IV). The mean difference in ASUI scores between visits with an EPAC in the prior period and visits without an EPAC was also 0.09 (Table V). For the EPAC components, the mean difference ranged from 0.08 to 0.16 (Table V). The mean differences in ASUI scores for the less serious EPACs of peak flow decrease and increased use of rescue inhalers were 0.08 and 0.10, respectively. For the more serious EPAC components of oral steroid use and unscheduled urgent care contact, the mean differences in ASUI scores were 0.16 and 0.15, respectively. These results support an MID of approximately 0.09.

Distribution-based results. The SD of baseline ASUI scores was 0.18 for the SIIVA trial and 0.16 for the SARA trial. On the basis of the ½ SD criteria as an estimate of MID, the MID of the ASUI is 0.09 and 0.08, respectively. The 1 SEM criteria produced MID estimates of 0.07 for the SARA sample and 0.09 for the SIIVA sample. Overall, from our study samples, we estimate the MID of the ASUI to be approximately 0.09.

DISCUSSION

The results of this study demonstrate that the ASUI, an asthma-specific utility index designed to summarize the frequency and severity of selected asthma-related symptoms,[8] has good psychometric properties in 2 groups of asthmatic patients. We confirmed the findings of Revicki et al[8] that ASUI scores have good construct validity, test-retest reliability, and discriminant validity. We also showed that baseline ASUI scores predict the occurrence of EPACs or asthma exacerbations in the subsequent 2 weeks. Patients with the lowest baseline ASUI scores were 40% more likely to have an EPAC and 8% more likely to have an asthma exacerbation over the next 2 weeks compared with those with the highest baseline ASUI scores. The ability to predict EPACs and asthma exacerbations suggests that the ASUI could be useful in guiding asthma therapy in clinical practice. In addition, we have shown that the ASUI is responsive to changes in asthma control. Using well-established anchor-based and statistical methods,[5,9,18,20] we estimated the MID of the ASUI to be approximately 0.09 points.

Some items on the ASUI are similar to those on other questionnaires that assess asthma control and asthma-related quality of life.[3,5,9,10] Asthma control as measured by the ACQ is a normative construct developed by physicians and validated against the physician's assessment of asthma.[3] Asthma-related quality-of-life instruments measure the extent to which asthma symptoms interfere with physical functioning in daily life.[5] The ASUI is complementary to these other tools by focusing on the frequency and severity of asthma symptoms. It is a patient preference–weighted scale and thus suitable for economic analyses that incorporate disability-adjusted life years.[8]

TABLE III. Predictive validity of the ASUI: relationship to the frequency of EPACs and exacerbations

	EPACs*		Exacerbations†	
Quartiles of ASUI	Frequency (%)	Relative risk (RR) (95% CI)	Frequency (%)	Relative risk (RR) (95% CI)
>0.95 (n = 321)	13	Reference = 1.00	4	Reference = 1.00
0.87-0.95 (n = 263)	24	1.13 (1.05-1.23)	4	1.00 (0.96-1.03)
0.74-0.86 (n = 290)	30	1.24 (1.13-1.35)	7	1.03 (0.99-1.07)
≤0.73 (n = 304)	40	1.44 (1.30-1.60)	11	1.08 (1.03-1.13)

RR, Relative risk.
*Any one of the following: (1) peak flow decrease of 30% or greater from personal best, (2) increased rescue medication use of greater than the average reported during the 2 weeks before randomization, (3) new or increased oral corticosteroids for asthma, and (4) an unscheduled use of health care for the treatment of asthma.
†Any one of the following: (1) new or increased oral corticosteroids for asthma and (2) an unscheduled health care encounter for treatment of asthma.

TABLE IV. Mean changes in ASUI scores as a function of changes in percent predicted FEV_1 and ACQ scores

	No. (patients)*	Mean change in ASUI score (95% CI)	*P* value
Changes in percent predicted FEV_1			
Better ($\Delta FEV_1 \geq 10\%$)	213 (163)	0.05 (0.03 to 0.07)	
Same ($-10\% \leq \Delta FEV_1 < 10\%$)	1657 (384)	0.01 (0.00 to 0.01)	
Worse ($\Delta FEV1 \leq -10\%$)	222 (170)	−0.03 (−0.05 to −0.02)	<.0001
Changes in ACQ† (ΔACQ)			
Better			
ΔACQ ≥ −1.5	76 (68)	0.32 (0.28 to 0.35)	
−1.0 ≤ ΔACQ < −1.5	111 (100)	0.15 (0.13 to 0.18)	
−0.5 ≤ ΔACQ < −1.0	255 (198)	0.09 (0.08 to 0.10)	
Same			
+0.5 > ΔACQ < −0.5	1254 (369)	0.00 (−0.00 to 0.01)	
Worse			
+1.0 > ΔACQ ≥ +0.5	233 (175)	−0.09 (−0.10 to −0.07)	
+1.5 > ΔACQ ≥ +1.0	78 (69)	−0.17 (−0.20 to −0.14)	
ΔACQ ≥ + 1.5	61 (53)	−0.32 (−0.36 to −0.28)	<.0001

Note: The MID for the ACQ is 0.5 points.
**No.* denotes frequency of events, and *patients* indicates the number of patients.
†*Better*, Decrease by 0.5 points or more; *same*, change by less than 0.5 points; *worse*, increase by 0.5 points or more.

TABLE V. Mean difference in ASUI scores by EPAC status for all visits

		ASUI		
	No. of EPACs (% visits)	Mean difference*	95% CI	*P* value*
Any EPACs	750 (35)	0.09	0.01-0.10	<.0001
EPAC components				
Peak flow decrease	426 (20)	0.08	0.06-0.10	<.0001
Rescue inhalers	414 (19)	0.10	0.01-0.12	<.0001
Oral steroid use	168 (8)	0.16	0.12-0.20	<.0001
Urgent care contact	103 (6)	0.15	0.11-0.20	<.0001

Two thousand one hundred fifty-five follow-up visit periods were evaluated among 390 participants.
*Mean difference in scores between visits with an EPAC in the prior period and those without an EPAC adjusted for visit period (repeated measures with independent correlation).

A key strength of this analysis is that data from 2 separate trials conducted at different time periods with different entry criteria and different interventions were used. However, because of the differing study designs, we were not able to perform the same validation analyses in both trials. It was necessary to use data from both studies to fully characterize the psychometric properties of the ASUI and to determine the MID. The SIIVA study included asthmatic patients with a wide range of clinical disease severity, but the ASUI was only administered at baseline,[13] and therefore test-retest reliability and longitudinal validity could not be assessed in this study population. Also, patients in the SIIVA trial had only 28 days of follow-up data, which might have limited the number of events, especially exacerbations. Nonetheless, because of the large population, we were able to demonstrate predictive validity based on the frequency of EPACs. In addition, ACQ and Mini AQLQ scores were not available for the SIIVA trial participants, and therefore construct validity could not be determined. The SARA trial, which included multiple ASUI measurements, as well as ACQ and Mini AQLQ scores, provided a good opportunity to determine responsiveness and construct validity.[11] Even though only patients with poorly controlled asthma were enrolled in the SARA trial, exploratory data analysis showed a skewed distribution of baseline ASUI scores, such that a majority of patients had very high scores and only a few patients had low scores.

A limitation of this study is the use of percent predicted FEV_1, ACQ scores, and EPACs as anchors for determining the MID. Data on other anchors, such as physician's global rating of asthma severity or control, were not available in this *post hoc* analysis.[9,10,18] Studies evaluating the psychometric properties of other asthma questionnaires have used changes in percent predicted FEV_1 and changes in ACQ scores as anchors to determine the MID.[9,10,18]

Generalizability to other patient populations is an important aspect of health utility tools.[20] The initial development and validation of the ASUI included asthmatic patients who were relatively well educated and mostly white.[8] The current scoring of

the ASUI in the United States is based on the multiattribute utility function that was originally derived by Revicki et al.[8] The preference weights, utility functions, and mean ASUI scores derived in the United States differ significantly from those obtained in other countries in Europe (Italy, France, and the United Kingdom).[22] However, the relative rank ordering of the mean ASUI scores by asthma severity is maintained.[22] In the current analysis we included participants with a good representation of women and racial minorities.[11,13] Data on education level or socioeconomic status were not available. However, many of the study sites were located in large urban centers in the United States that generally serve patients of low socioeconomic status. This study therefore expands the generalizability of the ASUI to a more diverse population of asthmatic patients. The ASUI score can be complex to calculate for an individual patient in the clinical setting compared with the Asthma Control Test,[4] and this could limit its routine use in clinical practice. However, computers can address this problem.

In summary, we demonstrated that the ASUI has good psychometric properties among adult asthmatic patients when used in the context of clinical trials in the United States. The MID of the ASUI in our population has been determined to be about 0.09 points. Further studies are needed to determine the psychometric properties of the ASUI in children and other demographic groups of the asthmatic population.

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Project Office, National Heart, Lung, and Blood Institute, Bethesda, Md: V. Taggart (project officer), G. Weinmann (DSMB secretary, airway branch chief)

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Clinical implications: The established MID of 0.09 points for the ASUI will aid clinicians in interpreting the results of clinical research and improve monitoring of asthma symptoms in clinical practice.

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Correction

With regard to the July 2012 article "Methacholine challenge test: Diagnostic characteristics in asthmatic patients receiving controller medications" (J Allergy Clin Immunol 2012;130:69-75), one of the participating centers was omitted from the list in Appendix E1. The authors acknowledge the contributions of their colleagues at New York Medical College: A. J. Dozor (principal investigator), S. Krishnan, (co-investigator), and I. Gherson (principal clinic coordinator).

Editorial

Adding measures to the asthma outcome measurement toolbox: New findings, new issues

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Key words: *Composite measures, asthma outcomes, asthma control, asthma symptoms, test-retest reliability*

The report of the 2010 Asthma Outcomes Workshop convened by the National Institutes of Health and the Agency for Healthcare Research and Quality was published earlier this year in a *Journal of Allergy and Clinical Immunology* supplement.[1] The workshop's premise, like that of 2 previous efforts,[2,3] was that "clinical research will highly benefit from standardization of major outcomes in terms of definition and assessment methodology" because this "will permit useful comparisons across interventional or observational studies and will allow more effective data sharing."

Workshop recommendations were made in 7 areas: biomarkers, pulmonary physiology, composite scores of asthma control, symptoms, exacerbations, health care use and costs, and disease effect on quality of life. In each area the report identified the currently available measures and measurement procedures for which there was published psychometric/performance data; evaluated the evidence as to their reliability, their validity for their intended purpose, and the adequacy of their other psychometric properties; identified information that was not available regarding their performance characteristics; identified measures that qualified as core (to be required) or supplementary measures for federally sponsored asthma clinical research; and determined whether new, better measurement instruments are needed. Two articles in this issue of the *Journal of Allergy and Clinical Immunology* speak to questions raised in the Workshop report's "Symptoms" and "Composite measures" chapters.[4,5]

The "Symptoms" report concluded that evaluation of symptoms is a core measurement that should be made in both experimental and observational asthma clinical research.[6] However, it did not recommend any specific measurement instrument or procedure. The Asthma Symptom Utility Index (ASUI), the most widely used retrospective symptom recall questionnaire for adults, was recommended as a supplementary measure for optional use depending on the aims of a particular research study. The ASUI was seen to have good reported measurement characteristics[7] but lacked information on fundamental psychometric properties. In this issue Bime et al[4] have provided substantial new information on the measurement properties of the ASUI using data from the Study of Acid Reflux and Asthma (SARA) and Safety of Inactivated Influenza Vaccine in Asthma (SIIVA) trials, including the ASUI's internal consistency reliability (coefficient α), test-retest reliability (intraclass correlation coefficient), construct validity (the correlations between the ASUI and both the Asthma Control Questionnaire [ACQ] and mini Asthma Quality of Life Questionnaire by using baseline scores of SARA participants), predictive validity (the ability of baseline ASUI scores to predict the frequency of episodes of poor asthma control within the subsequent 2 weeks), responsiveness to change in FEV_1 and ACQ scores of SARA trial participants assessed over consecutive study visits, and minimal clinically important score difference estimated by using anchor-based and distribution-based analyses.

The properties of the ASUI that these analyses reveal should increase confidence in the use of this instrument in asthma clinical research, although the method of assessing test-retest reliability using only the subset of patients who remained "stable" in terms of other concurrently assessed outcome measures, an unfortunately common practice, tends to overestimate the true value of the intraclass correlation coefficient.[8] Importantly, the ASUI is not encumbered by copyright restrictions, and although scoring is more complicated than a simple summation of responses, with appropriate computer support, this should be a minor consideration. The new ASUI performance results also come from US study samples with a higher proportion of persons of ethnic minority background and lower educational level than was the case in the sample from which the original preference and utility data and psychometric results were obtained.

Flood et al[9] found that preference weights, utility functions, and mean ASUI scores for European samples differed from those of the US developmental sample. Although this might appear to indicate some limitation of the ASUI scoring when it comes to international use, in fact, the samples all were very small ($n = 30$ each) and not selected to be representative of their respective countries. Sex, age, education, asthma severity, and comorbidities differed substantially among the samples of English, French, and Italian patients and differed from the US sample, and the preferences and ASUI means were not adjusted for these characteristics. Thus the evidence of country-related differences is much weaker than it might appear. As Bime et al[4] note, in both the US and European samples, ASUI scores were monotonically associated with asthma severity and had comparable levels of association with other asthma outcome measures. This finding is the most telling because the consistency of these associations is clearly a more important consideration in terms of the wider use of the ASUI than are the sample differences in observed preference and mean ASUI scores. Retaining the ability to compare study populations on the same measurement instrument and scale might well outweigh any theoretic advantage of scoring based on locally

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relevant preference weights and utilities. It is worth noting that the use of any utility function in scoring inherently ignores individual differences in preferences and utilities to gain the advantages associated with using average population preference values.

A new measure, the Asthma Disease Activity Score (ADAS), is reported in the article by Greenberg et al[5] and was not available for review in the workshop's "Composite measures" report.[10] Like all composite measures, the ADAS-6 combines information on multiple constructs typically obtained from multiple measurement procedures. The Asthma Control Questionnaire (ACQ), for example, requires spirometry to obtain FEV_1 values and a brief questionnaire to obtain information on multiple indicators of asthma control.[11] Combining reliable measures of relevant constructs can contribute to a measure that has greater predictive value with regard to other outcomes than any of its constituents alone, thus making an additional contribution to the outcome measurement toolbox. In fact, the weighting of the constituents of such composite scores is often derived from multivariate predictive modeling of the outcome of interest. The 6-item version (ADAS-6) provides a continuous score derived from measures of rescue β-agonist use (mean self-reported puffs per day from daily diary data), percent predicted FEV_1 (from office spirometry), symptoms (from the symptom domain score of the Juniper Asthma Quality of Life Questionnaire, or AQLQ),[11] reported nocturnal awakening (from daily diary data), and 2 variables: diurnal variability in rescue β-agonist use and diurnal variability in peak expiratory flow rate (from diurnal diary data). The latter 2 variables are omitted in the 4-item score (ADAS-4). The ADAS-6 has reasonable internal consistency reliability, is responsive to treatment, distinguishes well between asthma of different levels of severity (as does the ADAS-4), and is predictive of future exacerbations.

Concern about a potentially increased subject burden with the use of composite measures is lessened if the measurements that go into the composite are individually required for asthma research (eg, symptoms and FEV_1). The ADAS requires data from multiple sources, including one subscore of the AQLQ, which has use restrictions that require administration of the entire questionnaire.[12] Such a composite instrument faces a higher burden of proof of its value. Respondent burden is only partially addressed by testing a shortened (ADAS-4) version that avoids the need for patients to keep diurnal diaries. However, the ADAS could potentially use an alternative symptom measure, such as the ASUI. The ADAS was designed to measure disease activity, and although the authors caution that this is not the same construct as asthma control, the information going into the ADAS overlaps that of the Asthma Control Test and ACQ, both of which were recommended as core measures. Hence it will be important to determine whether the ADAS, with its additional use of diary data and differential weighting of its components, provides unique predictive information not provided by the Asthma Control Test and ACQ. Greenberg et al[5] have provided very useful information and insights that might lead to more effective composite measures and more efficient measurement of core asthma outcomes.

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