Published in final edited form as:
J Allergy Clin Immunol. 2012 March ; 129(3 Suppl): S34–S48. doi:10.1016/j.jaci.2011.12.983.

Asthma Outcomes: Exacerbations

Anne Fuhlbrigge, MD, MS,
Brigham & Women's Hospital

David Peden, MD,
University of North Carolina at Chapel Hill

Andrea J. Apter, MD,
University of Pennsylvania

Homer A. Boushey, MD,
University of California, San Francisco

Carlos Camargo Jr, MD, DrPH,
Massachusetts General Hospital

James Gern, MD,
University of Wisconsin

Peter W. Heymann, MD,
University of Virginia

Fernando D. Martinez, MD,
University of Arizona College of Medicine

David Mauger, PhD,
Penn State College of Medicine

William G. Teague, MD, and
University of Virginia

Carol Blaisdell, MD
National Heart, Lung, and Blood Institute

Abstract

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 (NIH) 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.

Corresponding author: Carol Blaisdell, MD, Division of Lung Diseases (DLD); National Heart, Lung, and Blood Institute (NHLBI); National Institutes of Health (NIH), 6701 Rockledge Drive, Bethesda Md 20892-7952, Telephone: 301-435-0219, blaisdellcj@nhlbi.nih.gov.
Anne Fuhlbrigge, (co-primary author)
David Peden, (co-primary author)

Methods—We utilized 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 an NIH-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 hospitalization, and (3) use of short-acting β-agonists (SABAs) 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. Further, they propose the development of a standardized, component-based definition of "exacerbation" with clear thresholds of severity for each component.

Keywords

Asthma exacerbations; severity of acute asthma; asthma outcomes; urgent asthma care

INTRODUCTION

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 single trial, and pool data for observational studies (eg, genetics, genomics, 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 [NIAID]; 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 proven, 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*[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 exacerbations outcomes are presented in this article.

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 (NAEPP) 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" (pp 374-5). 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" (p 69). 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" (p 61). 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 NIAID 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 details 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 (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 Composite Scores of Asthma Control article).

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
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 1–2 days of dexamethasone to achieve better adherence and similar outcomes.[89–91] The literature on the use of 1–2 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 (mg [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. Further, 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 usage 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, 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 and colleagues observed that having filled a prescription for systemic corticosteroid or having had a hospitalization during the prior 6 months was associated with increased risk of future admission for asthma.[103] 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. Forced expiratory volume in 1 second (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 SABA 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 IV], 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 IV), 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: 0–4, 5–11, 12–17, 18–64, and ≥65 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, play 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, while 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 (even with low acuity) 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. Further, 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, pathophysiological 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 typically 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 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 SABA 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 >3 to 12 puffs per day in pediatric studies and >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 SABA 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 (FACET) 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% 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% 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% 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 their 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. Further, 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. Further, 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 SABA, and response to SABA. 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 0–4 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 0–4 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 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 guidelines 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 (SaO_2), which, if less than 90%, can indicate serious respiratory distress. Lack of objective improvement in the physical examination following treatment with SABA 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 PEAK trial (Preventing Early Asthma in Kids),[30] participants aged 12–59 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 AIMS (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 PEAK trial, the AIMS 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 2–8 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 doses of SABA on 4 of 7 consecutive days or as having nighttime awakenings caused by asthma symptoms on ≥2 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 1–2 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 0–4 years.

Outcome measures for asthma exacerbation in c hildren aged 0–4 years—The subcommittee recommends that the core outcomes for asthma exacerbations in prospective clinical trials for children aged 0–4 years should be the same as for adolescents and adults:

- **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
- **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 per minute), hypoxemia (SaO_2, <90% predicted), cough, and retractions, and are included in a number of composite assessment tools, such as the Pediatric Asthma Severity Score (PASS),[3] Asthma Severity Score (ASS),[1] Clinical Asthma Score (CAS),[2] Preschool Respiratory Assessment Measure (PRAM),[5] Pulmonary Index (PI),[4] and Pulmonary Score (PS).[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 children 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] was identified that included children aged 5–11 years (with some variation in upper and lower age limits). Six additional studies included children aged 5–11 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 5–11 years was the use of systemic corticosteroids, followed by hospitalization or ED visit. The frequency and duration of SABA use; a drop 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 SABA 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 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 5–11 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 5–11 years is the same as that for children aged 0–4. 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 5–11 years because evidence in pediatric acute-care supports the use of only 1–2 days of injected 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 5–11 years are the same as those listed for children aged 0–4. FEV_1 is listed as a supplemental outcome for children age 5–11, when feasible, whereas FEV_1 is not a feasible measure for the 0–4 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.

Acknowledgments

Funding:

The Asthma Outcomes workshop was funded by contributions from 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 Development, the National Institute of Environmental Health Sciences, the Agency for Healthcare Research and Quality, and the Merck Childhood Asthma Network, as well as by a grant from the Robert Wood Johnson Foundation. Contributions from the National Heart, Lung, and Blood Institute, the National Institute of Allergy and Infectious Diseases, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institute of Environmental Health Sciences, and the US Environmental Protection Agency funded the publication of this article and for all other articles in this supplement.

Abbreviations

AIMS	Acute Intervention Management Strategies study
ASS	Asthma Severity Score
ATS	American Thoracic Society
CAS	Clinical Asthma Score
ED	Emergency department
EPR-3	Expert Panel Report 3
ERS	European Respiratory Society
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
GINA	Global Initiative for Asthma
ICU	Intensive care unit
mg	Milligram(s)
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PASS	Pediatric Asthma Severity Score
PEAK	Preventing Early Asthma in Kids trial
PEF	Peak expiratory flow
PI	Pulmonary Index
PRAM	Preschool Respiratory Assessment Measure
PS	Pulmonary Score

SABA	Short-acting β-agonist
SaO_2	Saturated with oxygen
SES	Socioeconomic status
UC	Urgent care

REFERENCES

1. Parkin PC, Macarthur C, Saunders NR, Diamond SA, Winders PM. Development of a clinical asthma score for use in hospitalized children between 1 and 5 years of age. J Clin Epidemiol. 1996; 49(8):821–825. Epub 1996/08/01. [PubMed: 8699199]
2. Bishop J, Carlin J, Nolan T. Evaluation of the properties and reliability of a clinical severity scale for acute asthma in children. J Clin Epidemiol. 1992; 45(1):71–76. Epub 1992/01/01. [PubMed: 1738014]
3. Gorelick MH, Stevens MW, Schultz TR, Scribano PV. Performance of a novel clinical score, the Pediatric Asthma Severity Score (PASS), in the evaluation of acute asthma. Acad Emerg Med. 2004; 11(1):10–18. Epub 2004/01/08. [PubMed: 14709423]
4. Becker AB, Nelson NA, Simons FE. The Pulmonary Index. Assessment of a clinical score for asthma. Am J Dis Child. 1984; 138(6):574–576. Epub 1984/06/01. [PubMed: 6720644]
5. Chalut DS, Ducharme FM, Davis GM. The Preschool Respiratory Assessment Measure (PRAM): a responsive index of acute asthma severity. J Pediatr. 2000; 137(6):762–768. Epub 2000/12/13. [PubMed: 11113831]
6. Smith SR, Baty JD, Hodge D 3rd. Validation of the Pulmonary Score: an asthma severity score for children. Acad Emerg Med. 2002; 9(2):99–104. Epub 2002/02/05. [PubMed: 11825832]
7. Mattke S, Martorell F, Sharma P, Malveaux F, Lurie N. Quality of care for childhood asthma: estimating impact and implications. Pediatrics. 2009; 123(Suppl 3):S199–S204. Epub 2009/04/16. [PubMed: 19221164]
8. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009; 180(1):59–99. Epub 2009/06/19. [PubMed: 19535666]
9. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Bethesda (MD): Global Initiative for Asthma (GINA); 2010. Updated 2010.
10. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma, Full Report 2007. Bethesda (MD): US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute; 2007.
11. Escribano A, Tutuncu A, Lohr I, Carlholm M, Polanowski T. Clinical comparability between the CFC and HFA budesonide pressurised metered-dose inhalers in paediatric patients with asthma: a randomised controlled trial. Curr Med Res Opin. 2006; 22(6):1085–1092. Epub 2006/07/19. [PubMed: 16846541]
12. Fleming DM, Crovari P, Wahn U, Klemola T, Schlesinger Y, Langussis A, et al. Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. Pediatr Infect Dis J. 2006; 25(10):860–869. Epub 2006/09/29. [PubMed: 17006278]
13. Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). Pediatrics. 2001; 108(2):E36. Epub 2001/08/03. [PubMed: 11483846]
14. Montuschi P, Mondino C, Koch P, Ciabattoni G, Barnes PJ, Baviera G. Effects of montelukast treatment and withdrawal on fractional exhaled nitric oxide and lung function in children with asthma. Chest. 2007; 132(6):1876–1881. Epub 2007/12/15. [PubMed: 18079221]

15. Morice AH, Peterson S, Beckman O, Kukova Z. Efficacy and safety of a new pressurised metered-dose inhaler formulation of budesonide/formoterol in children with asthma: a superiority and therapeutic equivalence study. Pulm Pharmacol Ther. 2008; 21(1):152–159. Epub 2007/03/23. [PubMed: 17376722]
16. Pedersen S, Engelstatter R, Weber HJ, Hirsch S, Barkai L, Emeryk A, et al. Efficacy and safety of ciclesonide once daily and fluticasone propionate twice daily in children with asthma. Pulm Pharmacol Ther. 2009; 22(3):214–220. Epub 2009/01/15. [PubMed: 19141327]
17. von Berg A, Jeena PM, Soemantri PA, Vertruyen A, Schmidt P, Gerken F, et al. Efficacy and safety of ipratropium bromide plus fenoterol inhaled via Respimat Soft Mist Inhaler vs. a conventional metered dose inhaler plus spacer in children with asthma. Pediatr Pulmonol. 2004; 37(3):264–272. Epub 2004/02/18. [PubMed: 14966821]
18. Fitzpatrick AM, Gaston BM, Erzurum SC, Teague WG. Features of severe asthma in school-age children: atopy and increased exhaled nitric oxide. J Allergy Clin Immunol. 2006; 118(6):1218–1225. Epub 2006/12/13. [PubMed: 17157650]
19. Szefler SJ, Mitchell H, Sorkness CA, Gergen PJ, O'Connor GT, Morgan WJ, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. Lancet. 2008; 372(9643):1065–1072. Epub 2008/09/23. [PubMed: 18805335]
20. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans RI, et al. Results of a home-based environmental intervention among urban children with asthma. N Engl J Med. 2004; 351(11):1068–1080. Epub 2004/09/10. [PubMed: 15356304]
21. Kattan M, Crain EF, Steinbach S, Visness CM, Walter M, Stout JW, et al. A randomized clinical trial of clinician feedback to improve quality of care for inner-city children with asthma. Pediatrics. 2006; 117(6):e1095–e1103. Epub 2006/06/03. [PubMed: 16740812]
22. Wright RJ, Mitchell H, Visness CM, Cohen S, Stout J, Evans R, et al. Community violence and asthma morbidity: the Inner-City Asthma Study. Am J Public Health. 2004; 94(4):625–632. Epub 2004/04/01. [PubMed: 15054016]
23. Gruchalla RS, Pongracic J, Plaut M, Evans RI, Visness CM, Walter M, et al. Inner City Asthma Study: relationships among sensitivity, allergen exposure, and asthma morbidity. J Allergy Clin Immunol. 2005; 115(3):478–485. Epub 2005/03/09. [PubMed: 15753892]
24. Pongracic JA, Visness CM, Gruchalla RS, Evans R 3rd, Mitchell HE. Effect of mouse allergen and rodent environmental intervention on asthma in inner-city children. Ann Allergy Asthma Immunol. 2008; 101(1):35–41. Epub 2008/08/07. [PubMed: 18681082]
25. O'Connor GT, Neas L, Vaughn B, Kattan M, Mitchell H, Crain EF, et al. Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol. 2008; 121(5):1133–1139. e1. Epub 2008/04/15. [PubMed: 18405952]
26. Szefler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy Clin Immunol. 2005; 115(2):233–242. Epub 2005/02/08. [PubMed: 15696076]
27. Sorkness CA, Lemanske RF Jr, Mauger DT, Boehmer SJ, Chinchilli VM, Martinez FD, et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. J Allergy Clin Immunol. 2007; 119(1):64–72. Epub 2006/12/05. [PubMed: 17140647]
28. Strunk RC, Bacharier LB, Phillips BR, Szefler SJ, Zeiger RS, Chinchilli VM, et al. Azithromycin or montelukast as inhaled corticosteroid-sparing agents in moderate-to-severe childhood asthma study. J Allergy Clin Immunol. 2008; 122(6):1138–1144. e4. Epub 2008/10/28. [PubMed: 18951618]
29. Guilbert TW, Morgan WJ, Krawiec M, Lemanske RF Jr, Sorkness C, Szefler SJ, et al. The Prevention of Early Asthma in Kids study: design, rationale and methods for the Childhood Asthma Research and Education network. Control Clin Trials. 2004; 25(3):286–310. Epub 2004/05/26. [PubMed: 15157730]
30. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N Engl J Med. 2006; 354(19): 1985–1997. Epub 2006/05/12. [PubMed: 16687711]

31. Bacharier LB, Phillips BR, Zeiger RS, Szefler SJ, Martinez FD, Lemanske RF Jr, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. J Allergy Clin Immunol. 2008; 122(6):1127–1135. e8. Epub 2008/11/01. [PubMed: 18973936]
32. The Childhood Asthma Management Program (CAMP): design, rationale, and methods. Childhood Asthma Management Program Research Group. Control Clin Trials. 1999; 20(1):91–120. Epub 1999/02/23. [PubMed: 10027502]
33. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. N Engl J Med. 2000; 343(15):1054–1063. Epub 2000/10/12. [PubMed: 11027739]
34. Strunk RC, Sternberg AL, Szefler SJ, Zeiger RS, Bender B, Tonascia J. Long-term budesonide or nedocromil treatment, once discontinued, does not alter the course of mild to moderate asthma in children and adolescents. J Pediatr. 2009; 154(5):682–687. Epub 2009/01/27. [PubMed: 19167726]
35. Schildcrout JS, Sheppard L, Lumley T, Slaughter JC, Koenig JQ, Shapiro GG. Ambient air pollution and asthma exacerbations in children: an eight-city analysis. Am J Epidemiol. 2006; 164(6):505–517. Epub 2006/06/27. [PubMed: 16798793]
36. Yu O, Sheppard L, Lumley T, Koenig JQ, Shapiro GG. Effects of ambient air pollution on symptoms of asthma in Seattle-area children enrolled in the CAMP study. Environ Health Perspect. 2000; 108(12):1209–1214. Epub 2001/01/03. [PubMed: 11133403]
37. Sharma S, Raby BA, Hunninghake GM, Soto-Quiros M, Avila L, Murphy AJ, et al. Variants in TGFB1, dust mite exposure, and disease severity in children with asthma. Am J Respir Crit Care Med. 2009; 179(5):356–362. Epub 2008/12/20. [PubMed: 19096005]
38. Bateman E, Karpel J, Casale T, Wenzel S, Banerji D. Ciclesonide reduces the need for oral steroid use in adult patients with severe, persistent asthma. Chest. 2006; 129(5):1176–1187. Epub 2006/05/11. [PubMed: 16685007]
39. Bousquet J, Boulet LP, Peters MJ, Magnussen H, Quiralte J, Martinez-Aguilar NE, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Respir Med. 2007; 101(12):2437–2446. Epub 2007/10/02. [PubMed: 17905575]
40. Busse W, Wolfe J, Storms W, Srebro S, Edwards L, Johnson M, et al. Fluticasone propionate compared with zafirlukast in controlling persistent asthma: a randomized double-blind, placebo-controlled trial. J Fam Pract. 2001; 50(7):595–602. Epub 2001/08/04. [PubMed: 11485708]
41. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol. 2001; 108(2):184–190. Epub 2001/08/10. [PubMed: 11496232]
42. Busse WW, Shah SR, Somerville L, Parasuraman B, Martin P, Goldman M. Comparison of adjustable- and fixed-dose budesonide/formoterol pressurized metered-dose inhaler and fixed-dose fluticasone propionate/salmeterol dry powder inhaler in asthma patients. J Allergy Clin Immunol. 2008; 121(6):1407–1414. 14 e1–14 e6. Epub 2008/05/06. [PubMed: 18455221]
43. Dusser D, Vicaut E, Lefrancois G. Double-blind, double-dummy, multinational, multicenter, parallel-group design clinical trial of clinical non-inferiority of formoterol 12 microg/unit dose in a b.i.d. regimen administered via an HFA-propellant-pMDI or a dry powder inhaler in a 12-week treatment period of moderate to severe stable persistent asthma in adult patients. Respiration. 2005; 72(Suppl 1):20–27. Epub 2005/05/26. [PubMed: 15915009]
44. Engelstatter R, Szlavik M, Gerber C, Beck E. Once-daily ciclesonide via metered-dose inhaler: similar efficacy and safety with or without a spacer. Respir Med. 2009; 103(11):1643–1650. Epub 2009/07/15. [PubMed: 19596188]
45. Huchon G, Magnussen H, Chuchalin A, Dymek L, Gonod FB, Bousquet J. Lung function and asthma control with beclomethasone and formoterol in a single inhaler. Respir Med. 2009; 103(1): 41–49. Epub 2008/11/04. [PubMed: 18977646]
46. Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy. 2005; 60(3):309–316. Epub 2005/02/01. [PubMed: 15679715]

47. Louis R, Joos G, Michils A, Vandenhoven G. A comparison of budesonide/formoterol maintenance and reliever therapy vs. conventional best practice in asthma management. Int J Clin Pract. 2009; 63(10):1479–1488. Epub 2009/09/23. [PubMed: 19769705]
48. Morice AH, Peterson S, Beckman O, Osmanliev D. Therapeutic comparison of a new budesonide/formoterol pMDI with budesonide pMDI and budesonide/formoterol DPI in asthma. Int J Clin Pract. 2007; 61(11):1874–1883. Epub 2007/09/25. [PubMed: 17887990]
49. Niphadkar P, Jagannath K, Joshi JM, Awad N, Boss H, Hellbardt S, et al. Comparison of the efficacy of ciclesonide 160 microg QD and budesonide 200 microg BID in adults with persistent asthma: a phase III, randomized, double-dummy, open-label study. Clin Ther. 2005; 27(11):1752–1763. Epub 2005/12/22. [PubMed: 16368446]
50. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. Am J Respir Crit Care Med. 2001; 164(8 Pt 1):1392–1397. Epub 2001/11/13. [PubMed: 11704584]
51. Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E, et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med. 2007; 356(20):2040–2052. Epub 2007/05/18. [PubMed: 17507703]
52. Papi A, Paggiaro P, Nicolini G, Vignola AM, Fabbri LM. Beclomethasone/formoterol vs fluticasone/salmeterol inhaled combination in moderate to severe asthma. Allergy. 2007; 62(10):1182–1188. Epub 2007/09/12. [PubMed: 17845589]
53. Papi A, Paggiaro PL, Nicolini G, Vignola AM, Fabbri LM. Beclomethasone/formoterol versus budesonide/formoterol combination therapy in asthma. Eur Respir J. 2007; 29(4):682–689. Epub 2006/11/17. [PubMed: 17107988]
54. Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. N Engl J Med. 1997; 337(20):1405–1411. Epub 1997/11/14. [PubMed: 9358137]
55. Pearlman DS, Berger WE, Kerwin E, Laforce C, Kundu S, Banerji D. Once-daily ciclesonide improves lung function and is well tolerated by patients with mild-to-moderate persistent asthma. J Allergy Clin Immunol. 2005; 116(6):1206–1212. Epub 2005/12/13. [PubMed: 16337447]
56. Peters SP, Prenner BM, Mezzanotte WS, Martin P, O'Brien CD. Long-term safety and asthma control with budesonide/formoterol versus budesonide pressurized metered-dose inhaler in asthma patients. Allergy Asthma Proc. 2008; 29(5):499–516. Epub 2008/08/13. [PubMed: 18694544]
57. Sears MR, Boulet LP, Laviolette M, Fitzgerald JM, Bai TR, Kaplan A, et al. Budesonide/formoterol maintenance and reliever therapy: impact on airway inflammation in asthma. Eur Respir J. 2008; 31(5):982–989. Epub 2008/01/25. [PubMed: 18216054]
58. Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur Respir J. 2001; 18(2):254–261. Epub 2001/09/01. [PubMed: 11529281]
59. Vincken W, Bantje T, Middle MV, Gerken F, Moonen D. Long-term efficacy and safety of ipratropium bromide plus fenoterol via Respimat® Soft Mist® Inhaler (SMI) versus a pressurised metered-dose inhaler in asthma. Clin Drug Investig. 2004; 24(1):17–28. Epub 2007/05/23.
60. Wenzel S, Busse W, Calhoun W, Panettieri R Jr, Peters-Golden M, Dube L, et al. The safety and efficacy of zileuton controlled-release tablets as adjunctive therapy to usual care in the treatment of moderate persistent asthma: a 6-month randomized controlled study. J Asthma. 2007; 44(4):305–310. Epub 2007/05/29. [PubMed: 17530530]
61. Zeiger RS, Bird SR, Kaplan MS, Schatz M, Pearlman DS, Orav EJ, et al. Short-term and long-term asthma control in patients with mild persistent asthma receiving montelukast or fluticasone: a randomized controlled trial. Am J Med. 2005; 118(6):649–657. Epub 2005/06/01. [PubMed: 15922697]
62. Lemanske RF Jr, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, et al. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. JAMA. 2001; 285(20):2594–2603. Epub 2001/05/23. [PubMed: 11368733]

63. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. Am J Respir Crit Care Med. 2007; 175(3):235–242. Epub 2006/09/26. [PubMed: 16998094]
64. Wise RA, Bartlett SJ, Brown ED, Castro M, Cohen R, Holbrook JT, et al. Randomized trial of the effect of drug presentation on asthma outcomes: the American Lung Association Asthma Clinical Research Centers. J Allergy Clin Immunol. 2009; 124(3):436–444. 44e1–44e8. Epub 2009/07/28. [PubMed: 19632710]
65. Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus SC, et al. Daily versus as-needed corticosteroids for mild persistent asthma. N Engl J Med. 2005; 352(15):1519–1528. Epub 2005/04/15. [PubMed: 15829533]
66. Deykin A, Wechsler ME, Boushey HA, Chinchilli VM, Kunselman SJ, Craig TJ, et al. Combination therapy with a long-acting beta-agonist and a leukotriene antagonist in moderate asthma. Am J Respir Crit Care Med. 2007; 175(3):228–234. Epub 2006/09/16. [PubMed: 16973987]
67. Drazen JM, Israel E, Boushey HA, Chinchilli VM, Fahy JV, Fish JE, et al. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. Asthma Clinical Research Network. N Engl J Med. 1996; 335(12):841–847. Epub 1996/09/19. [PubMed: 8778601]
68. Fish JE, Peters SP, Chambers CV, McGeady SJ, Epstein KR, Boushey HA, et al. An evaluation of colchicine as an alternative to inhaled corticosteriods in moderate asthma. National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Am J Respir Crit Care Med. 1997; 156(4 Pt 1):1165–1171. Epub 1997/11/14. [PubMed: 9351617]
69. Israel E, Chinchilli VM, Ford JG, Boushey HA, Cherniack R, Craig TJ, et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. Lancet. 2004; 364(9444):1505–1512. Epub 2004/10/27. [PubMed: 15500895]
70. Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr, Sorkness CA, et al. Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. JAMA. 2001; 285(20):2583–2593. Epub 2001/05/23. [PubMed: 11368732]
71. Lazarus SC, Chinchilli VM, Rollings NJ, Boushey HA, Cherniack R, Craig TJ, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. Am J Respir Crit Care Med. 2007; 175(8):783–790. Epub 2007/01/06. [PubMed: 17204725]
72. Martin RJ, Szefler SJ, Chinchilli VM, Kraft M, Dolovich M, Boushey HA, et al. Systemic effect comparisons of six inhaled corticosteroid preparations. Am J Respir Crit Care Med. 2002; 165(10):1377–1383. Epub 2002/05/23. [PubMed: 12016099]
73. Martin RJ, Szefler SJ, King TS, Kraft M, Boushey HA, Chinchilli VM, et al. The Predicting Response to Inhaled Corticosteroid Efficacy (PRICE) trial. J Allergy Clin Immunol. 2007; 119(1): 73–80. Epub 2007/01/09. [PubMed: 17208587]
74. Szefler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. J Allergy Clin Immunol. 2002; 109(3):410–418. Epub 2002/03/19. [PubMed: 11897984]
75. Olson LM, Radecki L, Frintner MP, Weiss KB, Korfmacher J, Siegel RM. At what age can children report dependably on their asthma health status? Pediatrics. 2007; 119(1):e93–e102. Epub 2007/01/04. [PubMed: 17200264]
76. Bateman ED, Izquierdo JL, Harnest U, Hofbauer P, Magyar P, Schmid-Wirlitsch C, et al. Efficacy and safety of roflumilast in the treatment of asthma. Ann Allergy Asthma Immunol. 2006; 96(5): 679–686. Epub 2006/05/30. [PubMed: 16729780]
77. Busse W, Raphael GD, Galant S, Kalberg C, Goode-Sellers S, Srebro S, et al. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomized clinical trial. J Allergy Clin Immunol. 2001; 107(3):461–468. Epub 2001/03/10. [PubMed: 11240946]
78. Busse WW, Israel E, Nelson HS, Baker JW, Charous BL, Young DY, et al. Daclizumab improves asthma control in patients with moderate to severe persistent asthma: a randomized, controlled trial. Am J Respir Crit Care Med. 2008; 178(10):1002–1008. Epub 2008/09/13. [PubMed: 18787222]

79. Morice AH, Hochmuth L, Ekelund J, Thoren A, Puterman AS. Comparable long-term safety and efficacy of a novel budesonide/formoterol pressurized metered-dose inhaler versus budesonide/formoterol Turbuhaler in adolescents and adults with asthma. Pulm Pharmacol Ther. 2008; 21(1): 32–39. Epub 2006/11/23. [PubMed: 17118686]
80. The safety of inactivated influenza vaccine in adults and children with asthma. N Engl J Med. 2001; 345(21):1529–1536. Epub 2002/01/17. [PubMed: 11794219]
81. Peters SP, Anthonisen N, Castro M, Holbrook JT, Irvin CG, Smith LJ, et al. Randomized comparison of strategies for reducing treatment in mild persistent asthma. N Engl J Med. 2007; 356(20):2027–2039. Epub 2007/05/18. [PubMed: 17507702]
82. Mastronarde JG, Anthonisen NR, Castro M, Holbrook JT, Leone FT, Teague WG, et al. Efficacy of esomeprazole for treatment of poorly controlled asthma. N Engl J Med. 2009; 360(15):1487–1499. Epub 2009/04/10. [PubMed: 19357404]
83. Naimi DR, Freedman TG, Ginsburg KR, Bogen D, Rand CS, Apter AJ. Adolescents and asthma: why bother with our meds? J Allergy Clin Immunol. 2009; 123(6):1335–1341. Epub 2009/04/28. [PubMed: 19395075]
84. National Heart Lung and Blood Institute. NAEPP Working Group report: considerations for diagnosing and managing asthma in the elderly. Bethesda (MD): US Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; 1996.
85. Allen SC, Jain M, Ragab S, Malik N. Acquisition and short-term retention of inhaler techniques require intact executive function in elderly subjects. Age and Ageing. 2003; 32(3):299–302. Epub 2003/05/02. [PubMed: 12720616]
86. Barr RG, Somers SC, Speizer FE, Camargo CA Jr. Patient factors and medication guideline adherence among older women with asthma. Archives of Internal Medicine. 2002; 162(15):1761–1768. Epub 2002/08/03. [PubMed: 12153380]
87. Pezzoli L, Giardini G, Consonni S, Dallera I, Bilotta C, Ferrario G, et al. Quality of spirometric performance in older people. Age and Ageing. 2003; 32(1):43–46. Epub 2003/01/24. [PubMed: 12540347]
88. Wolfenden LL, Diette GB, Skinner EA, Steinwachs DM, Wu AW. Gaps in asthma care of the oldest adults. Journal of the American Geriatrics Society. 2002; 50(5):877–883. Epub 2002/05/25. [PubMed: 12028175]
89. Gries DM, Moffitt DR, Pulos E, Carter ER. A single dose of intramuscularly administered dexamethasone acetate is as effective as oral prednisone to treat asthma exacerbations in young children. J Pediatr. 2000; 136(3):298–303. Epub 2000/03/04. [PubMed: 10700684]
90. Qureshi F, Zaritsky A, Poirier MP. Comparative efficacy of oral dexamethasone versus oral prednisone in acute pediatric asthma. J Pediatr. 2001; 139(1):20–26. Epub 2001/07/11. [PubMed: 11445789]
91. Greenberg RA, Kerby G, Roosevelt GE. A comparison of oral dexamethasone with oral prednisone in pediatric asthma exacerbations treated in the emergency department. Clin Pediatr. 2008; 47(8): 817–823. Epub 2008/05/10.
92. Messite J, Stellman SD. Accuracy of death certificate completion: the need for formalized physician training. JAMA. 1996; 275(10):794–796. Epub 1996/03/13. [PubMed: 8598597]
93. Lloyd-Jones DM, Martin DO, Larson MG, Levy D. Accuracy of death certificates for coding coronary heart disease as the cause of death. Ann Intern Med. 1998; 129(12):1020–1026. Epub 1998/12/29. [PubMed: 9867756]
94. Suissa S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2006; 173(8):842–846. Epub 2006/01/28. [PubMed: 16439716]
95. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II. Lancet. 2000; 355(9215):1582–1587. Epub 2000/05/23. [PubMed: 10821361]
96. Bland JM, Altman DG. Transformations, means, and confidence intervals. BMJ. 1996; 312(7038): 1079. Epub 1996/04/27. [PubMed: 8616417]

97. Lumley T, Diehr P, Emerson S, Chen L. The importance of the normality assumption in large public health data sets. Annu Rev Public Health. 2002; 23:151–169. Epub 2002/03/23. [PubMed: 11910059]

98. Altman DG, Bland JM. Quartiles, quintiles, centiles, and other quantiles. BMJ. 1994; 309(6960): 996. Epub 1994/10/15. [PubMed: 7950724]

99. Farber HJ. Risk of readmission to hospital for pediatric asthma. J Asthma. 1998; 35(1):95–99. Epub 1998/03/26. [PubMed: 9513588]

100. Bacharier LB, Dawson C, Bloomberg GR, Bender B, Wilson L, Strunk RC. Hospitalization for asthma: atopic, pulmonary function, and psychological correlates among participants in the Childhood Asthma Management Program. Pediatrics. 2003; 112(2):e85–e92. Epub 2003/08/05. [PubMed: 12897312]

101. Wever-Hess J, Kouwenberg JM, Duiverman EJ, Hermans J, Wever AM. Risk factors for exacerbations and hospital admissions in asthma of early childhood. Pediatr Pulmonol. 2000; 29(4):250–256. Epub 2000/03/29. [PubMed: 10738011]

102. Bloomberg GR, Trinkaus KM, Fisher EB Jr, Musick JR, Strunk RC. Hospital readmissions for childhood asthma: a 10-year metropolitan study. Am J Respir Crit Care Med. 2003; 167(8): 1068–1076. Epub 2003/04/10. [PubMed: 12684246]

103. Lieu TA, Quesenberry CP, Sorel ME, Mendoza GR, Leong AB. Computer-based models to identify high-risk children with asthma. Am J Respir Crit Care Med. 1998; 157(4 Pt 1):1173–1180. Epub 1998/05/01. [PubMed: 9563736]

104. Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. I. Assessing the economic impact. J Allergy Clin Immunol. 2001; 107(1):3–8. Epub 2001/01/10. [PubMed: 11149982]

105. Fuhlbrigge AL, Kitch BT, Paltiel AD, Kuntz KM, Neumann PJ, Dockery DW, et al. FEV(1) is associated with risk of asthma attacks in a pediatric population. J Allergy Clin Immunol. 2001; 107(1):61–67. Epub 2001/01/10. [PubMed: 11149992]

106. Fuhlbrigge AL, Guilbert T, Spahn J, Peden D, Davis K. The influence of variation in type and pattern of symptoms on assessment in pediatric asthma. Pediatrics. 2006; 118(2):619–625. Epub 2006/08/03. [PubMed: 16882815]

107. Krishnan JA, Riekert KA, McCoy JV, Stewart DY, Schmidt S, Chanmugam A, et al. Corticosteroid use after hospital discharge among high-risk adults with asthma. Am J Respir Crit Care Med. 2004; 170(12):1281–1285. Epub 2004/09/18. [PubMed: 15374842]

108. Gamble J, Fitzsimons D, Lynes D, Heaney LG. Difficult asthma: people's perspectives on taking corticosteroid therapy. J Clin Nurs. 2007; 16(3A):59–67. Epub 2007/05/24. [PubMed: 17518870]

109. Janson S, Becker G. Reasons for delay in seeking treatment for acute asthma: the patient's perspective. J Asthma. 1998; 35(5):427–435. Epub 1998/09/12. [PubMed: 9734350]

110. Lee TA, Fuhlbrigge AL, Sullivan SD, Finkelstein JA, Inui TS, Lozano P, et al. Agreement between caregiver reported healthcare utilization and administrative data for children with asthma. J Asthma. 2007; 44(3):189–194. Epub 2007/04/25. [PubMed: 17454336]

111. Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med. 2010; 363(18): 1715–1726. Epub 2010/10/29. [PubMed: 20979471]

112. Lemanske RF Jr, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. N Engl J Med. 2010; 362(11):975–985. Epub 2010/03/04. [PubMed: 20197425]

113. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med. 2011; 364(11):1005–1015. Epub 2011/03/18. [PubMed: 21410369]

114. Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbations predict excess lung function decline in asthma. Eur Respir J. 2007; 30(3):452–456. Epub 2007/06/01. [PubMed: 17537763]

115. Carr W, Zeitel L, Weiss K. Variations in asthma hospitalizations and deaths in New York City. Am J Public Health. 1992; 82(1):59–65. Epub 1992/01/01. [PubMed: 1536336]

116. Shields AE, Comstock C, Weiss KB. Variations in asthma care by race/ethnicity among children enrolled in a state Medicaid program. Pediatrics. 2004; 113(3 Pt 1):496–504. Epub 2004/03/03. [PubMed: 14993540]

117. Teach SJ, Guagliardo MF, Crain EF, McCarter RJ, Quint DM, Shao C, et al. Spatial accessibility of primary care pediatric services in an urban environment: association with asthma management and outcome. Pediatrics. 2006; 117(4 Pt 2):S78–S85. Epub 2006/06/17. [PubMed: 16777835]
118. Homer CJ, Szilagyi P, Rodewald L, Bloom SR, Greenspan P, Yazdgerdi S, et al. Does quality of care affect rates of hospitalization for childhood asthma? Pediatrics. 1996; 98(1):18–23. Epub 1996/07/01. [PubMed: 8668406]
119. Ash M, Brandt S. Disparities in asthma hospitalization in Massachusetts. Am J Public Health. 2006; 96(2):358–362. Epub 2005/12/29. [PubMed: 16380574]
120. McConnochie KM, Russo MJ, McBride JT, Szilagyi PG, Brooks AM, Roghmann KJ. Socioeconomic variation in asthma hospitalization: excess utilization or greater need? Pediatrics. 1999; 103(6):e75. Epub 1999/06/03. [PubMed: 10353972]
121. Roy SR, Milgrom H. Managing outpatient asthma exacerbations. Curr Allergy Asthma Rep. 2010; 10(1):56–66. Epub 2010/04/29. [PubMed: 20425515]
122. Harrison TW, Oborne J, Newton S, Tattersfield AE. Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. Lancet. 2004; 363(9405):271–275. Epub 2004/01/31. [PubMed: 14751699]
123. Oborne J, Mortimer K, Hubbard RB, Tattersfield AE, Harrison TW. Quadrupling the dose of inhaled corticosteroid to prevent asthma exacerbations: a randomized, double-blind, placebo-controlled, parallel-group clinical trial. Am J Respir Crit Care Med. 2009; 180(7):598–602. Epub 2009/07/11. [PubMed: 19590019]
124. Savenije OE, Granell R, Caudri D, Koppelman GH, Smit HA, Wijga A, et al. Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. J Allergy Clin Immunol. 2011; 127(6):1505–1512. e14. Epub 2011/03/18. [PubMed: 21411131]
125. Gonem S, Desai D, Siddiqui S, Brightling CC. Evidence for phenotype-driven treatment in asthmatic patients. Curr Opin Allergy Clin Immunol. 2011; 11(4):381–385. Epub 2011/06/15. [PubMed: 21670666]
126. Bhakta NR, Woodruff PG. Human asthma phenotypes: from the clinic, to cytokines, and back again. Immunol Rev. 2011; 242(1):220–232. Epub 2011/06/21. [PubMed: 21682748]
127. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. J Allergy Clin Immunol. 2011; 127(2):382–389. e1–e13. Epub 2011/01/05. [PubMed: 21195471]
128. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med. 2010; 181(4):315–323. Epub 2009/11/07. [PubMed: 19892860]
129. Kiley J, Smith R, Noel P. Asthma phenotypes. Curr Opin Pulm Med. 2007; 13(1):19–23. Epub 2006/11/30. [PubMed: 17133120]
130. Rosi E, Ronchi MC, Grazzini M, Duranti R, Scano G. Sputum analysis, bronchial hyperresponsiveness, and airway function in asthma: results of a factor analysis. J Allergy Clin Immunol. 1999; 103(2 Pt 1):232–237. Epub 1999/02/09. [PubMed: 9949313]
131. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med. 2005; 171(2):129–136. Epub 2004/10/27. [PubMed: 15502112]
132. Leone FT, Mauger EA, Peters SP, Chinchilli VM, Fish JE, Boushey HA, et al. The utility of peak flow, symptom scores, and beta-agonist use as outcome measures in asthma clinical research. Chest. 2001; 119(4):1027–1033. Epub 2001/04/11. [PubMed: 11296165]
133. Cote J, Cartier A, Malo JL, Rouleau M, Boulet LP. Compliance with peak expiratory flow monitoring in home management of asthma. Chest. 1998; 113(4):968–972. Epub 1998/04/29. [PubMed: 9554633]

TABLE I

Recommendations for classifying a sthma exacerbation outcome measures for NIH-initiated clinical research in adult (aged ≥18 years) and adolescent (aged 12–17 years) 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		

ED, emergency department; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *ICU*, intensive care unit; *NIH*, National Institutes of Health; *SABA*, short-acting β-agonist; *SES*, socioeconomic status; *UC*, urgent care.

*Observational study designs include cohort, case control, cross sectional, retrospective reviews, and genome-wide association studies (GWAS), 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 component 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.

ED, emergency department; *SABA*, short-acting β-agonist; *UC*, urgent care.

TABLE III

Recommendations for classifying a sthma exacerbation outcome measures for NIH-initiated clinical research in pediatric populations (aged 0–4 and 5–11 years)

	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

	Characterization of study population for prospective clinical trials (ie, baseline information)	Prospective clinical trial efficacy/effectiveness outcomes	Observational study outcomes*
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] ; *ED*, emergency department; *FeNO*, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; *ICU*, intensive care unit; *NIH*, National Institutes of Health; *PASS*, Pediatric Asthma Severity Score[3]; *PI*, Pulmonary Index[4]; *PRAM*, Preschool Respiratory Assessment Measure[5]; *PS*, Pulmonary Score[6]; *SABA*, short-acting β-agonist; *SES*, socioeconomic status; *UC*, urgent care.

*Observational study designs include cohort, case control, cross sectional, retrospective reviews, and genome-wide association studies (GWAS), 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 SABA is a more commonly employed 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 physiological 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.

FeNO, fractional exhaled nitric oxide; *FEV1*, forced expiratory volume in 1 second; *SABA*, short-acting β-agonist.

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)	Number 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] ; *ED*, emergency department; *mg*, milligram(s); *PASS*, Pediatric Asthma Severity Score[3]; *PI*, Pulmonary Index[4] ; *PRAM*, Preschool Respiratory Assessment Measure[5]; *PS*, Pulmonary Score[6]