Asthma Outcomes: Asthma Symptoms

Jerry A. Krishnan, MD, PhD,
University of Illinois at Chicago

Robert F. Lemanske Jr, MD,
University of Wisconsin

Glorisa J. Canino, MD, PhD,
University of Puerto Rico

Kurtis S. Elward, MD, MPH,
Family Medicine of Albermarle

Meyer Kattan, MD,
Columbia University Medical Center

Elizabeth C. Matsui, MD, MHS,
Johns Hopkins University

Herman Mitchell, PhD,
Rho Federal Systems Division, Inc

E. Rand Sutherland, MD, MPH, and
National Jewish Health

Michael Minnicozzi, PhD
National Institute of Allergy and Infectious Diseases

Abstract

Background—Respiratory symptoms are commonly used to assess the impact of patient-centered interventions.

Objective—At the request of National Institutes of Health (NIH) institutes and other federal agencies, an expert group was convened to propose which measurements of asthma symptoms should be used as a standardized measure in future clinical research studies.

Methods—Asthma symptom instruments were classified as daily diaries (prospectively recording symptoms between research visits) or retrospective questionnaires (completed at research visits). We conducted a systematic search in PubMed and a search for articles that cited

Corresponding author: Michael Minnicozzi, PhD, Division of Allergy, Immunology, and Transplantation (DAIT); National Institute of Allergy and Infectious Diseases (NIAID); National Institutes of Health (NIH), 6610 Rockledge Drive, Bethesda, Md 20892, Telephone: 301-496-8973, minnicozzm@niaid.nih.gov.
Jerry A. Krishnan, (co-primary author), Robert F. Lemanske Jr, (co-primary author)

key studies describing development of instruments. We classified outcome instruments as either core (required in future studies), supplemental (used according to study aims and standardized), or emerging (requiring validation and standardization). This work was discussed at an NIH-organized workshop in March 2010 and finalized in September 2011.

Results—Four instruments (3 daily diaries, 1 for adults and 2 for children; and 1 retrospective questionnaire for adults) were identified. Minimal clinically important differences have not been established for these instruments, and validation studies were only conducted in a limited number of patient populations. Validity of existing instruments may not be generalizable across racial-ethnic or other subgroups.

Conclusions—An evaluation of symptoms should be a core asthma outcome measure in clinical research. However, available instruments have limitations that preclude selection of a core instrument. The working group participants propose validation studies in diverse populations, comparisons of diaries versus retrospective questionnaires, and evaluations of symptom assessment alone versus composite scores of asthma control.

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.[5] Several National Institutes of Health (NIH) institutes that support asthma research (the National Heart, Lung, and Blood Institute; National Institute of Allergy and Infectious Diseases; National Institute of Environmental Health Sciences; and 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*[6] (hereafter referred to as the *ATS/ERS Statement*) as a starting point and updated, expanded, or modified its recommendations as the subcommittee deemed appropriate. Each subcommittee produced a report that was discussed, modified, and adopted by the Asthma Outcomes Workshop that took place in Bethesda, Md, on March 15 and 16, 2010. The reports were revised accordingly and finalized in September 2011. The workshop's recommendations in regards to asthma symptoms are presented in this article.

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

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

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

REVIEW OF SYMPTOMS AS AN OUTCOME MEASURE

Definitions

Asthma symptoms are measured by patient or caregiver report, via self-administered paper or electronic diaries or questionnaires, or interviewer-administered questionnaires. A variety of considerations influence the measurement of asthma symptoms in research studies. For

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

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

- To identify and evaluate the validity of daily symptom diaries used in asthma clinical research

- To identify and evaluate the validity of retrospective symptom questionnaires used in asthma clinical research

- To determine whether daily symptom diaries add value in documenting the adequacy of asthma treatment (ie, control of symptoms), compared with retrospective symptom questionnaires

Search Methodology

The literature search was conducted in 2 stages:

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

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

OR

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

OR

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

OR

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

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

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

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

Search Results

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

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

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

- Symptoms used as primary or secondary endpoint in study

- Objective of study

- Study design

- Description of symptom instrument (including source, if cited)

- Study sample description (including age, sex, race/ethnicity, income)

- Asthma severity (including severity score if available)

- Sample size

- State (if US) or country

- Description of symptom outcome measure based on key article

- Study results related to symptoms, lung function, biomarkers, exacerbations, acute care utilization (eg, emergency department [ED] visits), medication use

Validity and Reliability of Instruments

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

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

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

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

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

Medical and Scientific Value

The subcommittee considers symptoms to be a significant manifestation of asthma and an important patient-oriented outcome. However, the subcommittee's review of instruments to measure symptoms raised significant questions regarding their classification as core,

supplemental, or emerging outcome measures. Despite the frequent use of symptom diaries or questionnaires, it is not clear how much additional information they contribute either independently or collectively to other outcome measures, such as pulmonary function, biomarkers, respiratory exacerbations, or combinations of outcome measures (eg, composite scores of asthma control, which include symptoms as well as other manifestations of asthma, such as the Asthma Control Test [see the Composite Scores of Asthma Control article]) that are commonly assessed in clinical research. In addition, many trials employ "homemade" instruments to assess symptoms (ie, newly derived endpoints, such as asthma-free days, based on alternative analysis of the data collected by the instruments) that have not been formally validated as an outcome measure, nor described in published manuscripts, raising questions about the value of such assessments and precluding comparisons across studies. There is also limited validation of instruments in diverse populations, which is problematic given differences in symptom perception and reporting across different patient subgroups.[8–10] Further, evidence of minimal clinically important difference (MCID) in a change in symptoms in longitudinal studies is largely lacking. Finally, the routine use of either symptom diaries or questionnaires introduces a level of participant and study personnel (eg, study coordinator) burden that needs to be evaluated in the context of the value of that information relative to other indices in asthma health. In short, the researcher must consider whether this burden is really worth the effort.

Future Directions and Key Research Questions

1. Titles, abstracts, and key words of published studies rarely indicate whether a study collected information on asthma symptoms, how this information was collected (ie, the name of the instrument), or how the information was used. The methods sections of these studies also frequently fail to describe this information or do so only inadequately. As a result, the key word-based literature search identified few instruments that assess symptoms. The name of the instrument(s) used to measure symptoms should be reported in the methods section; information about the validity of such instruments also should be reported, where available. If the abstract includes information about asthma symptoms, the instrument used to measure symptoms should be identified in the abstract as well.

2. Studies are needed that compare the added value of measuring symptoms alone with measuring them as part of other outcomes; ie, asthma composite scores such as the Asthma Control Test or Asthma Control Questionnaire (see the Composite Scores of Asthma Control article).

3. Completing daily diaries imposes a substantial burden on study participants and research staff; eg, ensuring that diaries are completed and data are entered. Studies are needed to directly compare the value of daily diaries with that of retrospective questionnaires in asthma clinical research.

4. Instruments to measure asthma symptoms have not been tested adequately in diverse patient populations (eg, populations that differ by race/ethnicity, socioeconomic status [SES], or health literacy). Given the burden of asthma in particular subpopulations (eg, racial/minorities and those with low SES and low health literacy), existing instruments need to be validated in these groups.

REVIEW OF SPECIFIC ASTHMA SYMPTOM QUESTIONNAIRES

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

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

Summary—

1. Although parent/caregiver completed reports of children's asthma symptoms are valuable, self-reported information has inherent value in accurately assessing the child's experience and response to treatment. The electronic Pediatric Asthma Symptom Diary Scale (PASDS) is therefore of significant interest.

2. The electronic PASDS is the only symptom instrument specifically validated with the use of an electronic diary, which may improve data quality.

3. The scoring scale seems inadequate in that the mean scores were all well below 1.0 on a scale of 0 to 5 for the daytime symptom scale. Thus, there may be a floor effect that limits the value of this instrument.

4. Limited information regarding the study population used to develop and validate the instrument suggests the results may not be broadly applicable in children aged 6 to 14 years (the age range of the population studied).

5. More information about the psychometric properties is needed.

6. Recommendation for use in NIH-initiated asthma studies: The subcommittee recommends classifying the electronic PASDS as an emerging instrument for the symptom outcome measure.

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

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

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

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

Validity—The instrument scores were not significantly correlated with the measure of forced expiratory volume in 1 second (FEV_1). The authors make the case that FEV_1 has not been found to correlate with changes in asthma symptoms, but the references they cite actually provide little support for their assertions. For example, their citation of McFadden et al[12] pertains only to acute (emergent) exacerbations, not to the population they studied. The mean FEV_1 was 82.5% in the "stable" group. Thus, airflow obstruction was considerably more severe in a subgroup of study participants than in other studies of children; eg, studies of mild persistent asthma in which the FEV_1 is over 93% predicted value (Childhood Asthma Management Program and Personalized Assessment and Control Tool).[11, 13] The lower FEV_1 in this subgroup of participants may help explain why symptom scores were not associated with FEV_1: there is evidence that blunted perception of airflow obstruction occurs in patients with more severe disease.[8, 14] All 3 daytime symptom questionnaires discriminated between stable and new onset/worse groups at baseline, but the short duration of the trial was insufficient for evaluation of longitudinal validity.

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

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

Practicality and risk—The diary seems very easy to use in the target population. The questions are simple and should be easy to use with children 6–14 years old (Fleisch Reading Ease scale of 2nd grade level). Use of an electronic diary is a considerable strength of this instrument; it may help improve accuracy and completeness of the symptom diary, but this improvement would need to be demonstrated in a more broadly selected population. Use of this instrument has minimal risk.

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

Summary—

1. The Pediatric Asthma Caregiver Diary (PACD) was developed for use by caregivers of children aged 2 to 5 years with persistent asthma, and it has relatively good measurement characteristics in this population.

2. It is not known whether results are generalizable across asthma severity categories or demographic groups that vary from the study population, which was largely white.

3. Although the maximum score was 5 for the diary, participants generally reported scores of 0 or 1. Mean scores that combined symptom and activity scores were almost always less than 1. Although results seem to be sensitive to treatment, there may be a floor effect that limits the value of this instrument.

4. As with all caregiver/parent-reported symptoms, caregivers or parents may underreport symptoms because of a desire to appear to have taken good care of their child's asthma.

5. Recommendation for use in NIH-initiated clinical trials: The subcommittee recommends classifying the PACD as a supplemental instrument for symptom outcome measure.

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

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

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

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

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

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

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

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

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

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

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

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

Summary—

1. The Daytime Symptom Diary Scale and Nocturnal Diary Scale have relatively good measurement characteristics for use in adults with asthma.

2. Results seem to be sensitive to treatment.

3. It is not known whether results are generalizable across asthma severity categories or demographic groups that vary from the study population.

4. Recommendation for use in NIH-initiated clinical trials: The subcommittee recommends these scales as a supplemental outcome.

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

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

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

Range of values and scoring—The Daytime Symptom Diary Scale ranges from 0 (none of the time) to 6 (all of the time). The Nocturnal Diary Scale ranges from 0 (no awakening with asthma symptoms) to 3 (awake all night). Daytime scores are computed as the average of the 4 questions on the daytime symptom scale and the weekly score as the average of the daily daytime scale scores. Nocturnal scores are computed in a similar manner. A decrease in the weekly score for the daytime and nocturnal scales indicates an

improvement in asthma symptoms. The change from baseline in the asthma scale scores is computed as the difference between the average score from the last 2 weeks of the placebo run-in period and the last 2 weeks of the active treatment phase in the 2 clinical trials.

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

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

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

Responsiveness—The responsiveness of the daytime and nocturnal diary scales varied with drug treatment. The daytime and nocturnal scales were responsive to change across the drug dose groups in 1 study (*p*-value for trend < 0.05), but not significantly different between study treatment and placebo in the other study ($p > 0.10$). Consistent with the responsiveness of the symptom scales, the average change in the asthma measures of FEV_1, PEFR, and SABA inhaler use showed greater improvements in the drug-treated groups than in the placebo-treated group.

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

Asthma Symptom Utility Index (Developed by D.A. Revicki)[1]

Summary—

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

2. The ASUI is 1 of the most tested symptom measures reported in the literature, including use in French, English, and Italian adults. The ASUI has good measurement characteristics for use in adults with asthma.

3. Results indicate that the ASUI is sensitive to change over different levels of severity.

4. The ASUI scoring requires a complex calculation of a product of 5 values, weighted by patient preferences.

5. The scale is constructed based on weights assigned to different preferences; these weights might not be generalizable to other groups diverse in ethnicity, culture, or SES.

6. There is a need for studies, particularly for this measure, that can determine empirically which scores are associated with clinically significant improvement.

7. Recommendation for use in NIH-initiated clinical trials: The subcommittee recommends classifying the ASUI as a supplemental outcome.

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

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

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

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

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

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

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

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

Validity—The convergent validity or correlation of the scale with other measures of the same or similar nature was assessed by comparing the ASUI with 2 symptom severity measures: the Physician Severity Rating Scale (PSRS) and the Asthma Disease Severity Scale (ADSS). Both scales were previously found to be reliable and valid in determining asthma severity. The PSRS is a physician global assessment of the severity of asthma on a scale of 1 (mild) to 6 (severe) based on the patient's pulmonary function tests and medical and symptom history information from the asthma medical history instrument[1] component of the PSRS. The ADSS is a composite of resource use, spirometry, and symptoms, including ED visits during the past 12 months (1); hospitalizations during the past 12 months (1); FEV_1 percent predicted <70%; chronic cough or chronic phlegm; chronic wheeze; chronic breathlessness; and chronic nighttime symptoms. The ASUI scale discriminated well across severity levels using the PSRS ($p < 0.0001$) and the ADSS ($p < 0.001$) as comparisons.

Construct validity was assessed by comparing the ASUI with lung functioning, the Health Utilities Index (HUI), and Juniper's Asthma Quality of Life Questionnaire (AQLQ).[1] The results of the comparison with lung function (construct validity) showed significant

association between ASUI severity scores and FEV1 percent predicted ($r = 0.27$; $p < 0.01$) and FEV_1/forced vital capacity ($r = 0.27$; $p < 0.001$). The ASUI was significantly correlated with the HUI ($r = 0.32$; $p < 0.001$). There were also strong correlations between the ASUI and the overall score of the AQLQ (0.77), the activity limitations score (0.59), symptoms (0.85), emotional function (0.63), and environmental exposure (0.70).

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

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

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

The generalizability of the scale is also unclear. The scale's construction is based on weights assigned to different preferences that might not be generalizable to other groups. The participants in the study used to validate the scale had the following demographic characteristics: mean age (± SD) 34.7 ± 10.7 years; 59% female, 79% white, 17% black, and 3% Asian American. ASUI scores were unrelated to age (in adults), sex, and educational level. The scale has been validated only for adults; no pediatric analogue exists. In addition, evidence exists that the algorithms used to score the ASUI would need to be modified for each racial/ethnic group. The results of the international validation of the scale in Italy, France, and the UK showed variability in the scores across countries, particularly for medication side effects.[25] Variability also was observed in the rank order of the multisymptom states. Differences were identified across countries in deriving ASUI weighting algorithms, which are necessary to develop the table of scores used to arrive at an overall score. When the combined data (from all countries) were analyzed, the authors were able to fit the multiplicative multi-attribute utility function and derive ASUI scores based on the algorithm. However, a new algorithm had to be derived for each country because of cross-national differences (especially in France and Italy) in the relative importance or value

placed on the same symptoms. Differences were particularly evident regarding the severe wheeze state and the moderate level multisymptom states (involving cough and wheeze or dyspnea). US participants tended to rate these symptom states as more severe than did those from Italy and France, whereas UK participants fell in the middle. The authors recommended that the stability of the weights used for the scoring algorithms be tested in future studies for SES and culture.

ADDITIONAL CONSIDERATIONS

Electronic Diaries

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

SYMPTOM DERIVATIVES

Symptom-Free Days

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

Symptoms as a Component of Composite Indices

A variety of indices have been used in clinical trials that include symptoms as 1 component of a larger index, such as *episode-free days*,[18, 47] *asthma control days*,[13, 48] and *maximum symptom days*[49] or *asthma control*[50, 51] These indices record not only symptom frequency and/or severity, but also may record events such as lost sleep, changes in activities of daily living, inpatient admissions, and ED and clinic visits, among others, as well as evaluating lung function (eg, peak expiratory flow [PEF]). Thus, symptoms are recorded as part of a more global composite index that is used to evaluate asthma control and response to therapy. These indices have varying degrees of validation (see the Composite Scores of Asthma Control article). When symptom scores are measured in these ways, it is not possible to disentangle their individual value from that of the entire index as an outcome measure. Research is needed to compare the value of measuring symptoms alone to symptoms as a part of a composite index.

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

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

Acknowledgments

Abbreviations

ADSS	Asthma Disease Severity Scale
AQLQ	Asthma Quality of Life Questionnaire
ASUI	Asthma Symptom Utility Index
ATS	American Thoracic Society
ED	Emergency department
ERS	European Respiratory Society
FEV$_1$	Forced expiratory volume in 1 second
HUI	Health Utilities Index
ICC	Intra-class correlation coefficient
MCID	Minimal clinically important difference
NIH	National Institutes of Health
PACD	Pediatric Asthma Caregiver Diary
PASDS	Pediatric Asthma Symptom Diary Scale
PERF	Peak expiratory flow rate
PSRS	Physician Severity Rating Scale
QOL	Quality of life
SABA	Short-acting β-agonist
SES	Socioeconomic status
SFD	Symptom-free day
UC	Urgent care

REFERENCES

1. Revicki DA, Leidy NK, Brennan-Diemer F, Sorensen S, Togias A. Integrating patient preferences into health outcomes assessment: the multiattribute Asthma Symptom Utility Index. Chest. 1998; 114(4):998–1007. Epub 1998/10/29. [PubMed: 9792568]

2. Santanello NC, Barber BL, Reiss TF, Friedman BS, Juniper EF, Zhang J. Measurement characteristics of two asthma symptom diary scales for use in clinical trials. Eur Respir J. 1997; 10(3):646–651. Epub 1997/03/01. [PubMed: 9072999]

3. Santanello NC, Demuro-Mercon C, Davies G, Ostrom N, Noonan M, Rooklin A, et al. Validation of a pediatric asthma caregiver diary. J Allergy Clin Immunol. 2000; 106(5):861–866. Epub 2000/11/18. [PubMed: 11080707]

4. Santanello NC, Davies G, Galant SP, Pedinoff A, Sveum R, Seltzer J, et al. Validation of an asthma symptom diary for interventional studies. Arch Dis Child. 1999; 80(5):414–420. Epub 1999/04/20. [PubMed: 10208944]

5. 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]

6. 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]

7. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. Stroke. 2007; 38(3):1091–1096. Epub 2007/02/03. [PubMed: 17272767]

8. Davis SQ, Permutt Z, Permutt S, Naureckas ET, Bilderback AL, Rand CS, et al. Perception of airflow obstruction in patients hospitalized for acute asthma. Ann Allergy Asthma Immunol. 2009; 102(6):455–461. Epub 2009/06/30. [PubMed: 19558002]

9. Bijl-Hofland ID, Cloosterman SG, Folgering HT, Akkermans RP, van Schayck CP. Relation of the perception of airway obstruction to the severity of asthma. Thorax. 1999; 54(1):15–19. Epub 1999/05/27. [PubMed: 10343625]

10. Hardie GE, Janson S, Gold WM, Carrieri-Kohlman V, Boushey HA. Ethnic differences: word descriptors used by African-American and white asthma patients during induced bronchoconstriction. Chest. 2000; 117(4):935–943. Epub 2000/04/18. [PubMed: 10767221]

11. 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]

12. McFadden ER Jr. Clinical physiologic correlates in asthma. J Allergy Clin Immunol. 1986; 77(1 Pt 1):1–5. Epub 1986/01/01. [PubMed: 3944367]

13. 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]

14. Motomura C, Odajima H, Tezuka J, Harada J, Okada K, Nishima S. Perception of dyspnea during acetylcholine-induced bronchoconstriction in asthmatic children. Ann Allergy Asthma Immunol. 2009; 102(2):121–124. Epub 2009/02/24. [PubMed: 19230462]

15. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. Qual Life Res. 1996; 5(1):35–46. Epub 1996/02/01. [PubMed: 8901365]

16. Knorr B, Nguyen HH, Kearns GL, Villaran C, Boza ML, Reiss TF, et al. Montelukast dose selection in children ages 2 to 5 years: comparison of population pharmacokinetics between children and adults. J Clin Pharmacol. 2001; 41(6):612–619. Epub 2001/06/14. [PubMed: 11402629]

17. Bacharier LB, Phillips BR, Bloomberg GR, Zeiger RS, Paul IM, Krawiec M, et al. Severe intermittent wheezing in preschool children: a distinct phenotype. J Allergy Clin Immunol. 2007; 119(3):604–610. Epub 2007/03/06. [PubMed: 17336610]

18. 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]

19. 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]

20. Skoner DP, Greos LS, Kim KT, Roach JM, Parsey M, Baumgartner RA. Evaluation of the safety and efficacy of levalbuterol in 2–5-year-old patients with asthma. Pediatr Pulmonol. 2005; 40(6):477–486. Epub 2005/09/30. [PubMed: 16193496]

21. 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]

22. 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]

23. 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]

24. Hanania NA, Sockrider M, Castro M, Holbrook JT, Tonascia J, Wise R, et al. Immune response to influenza vaccination in children and adults with asthma: effect of corticosteroid therapy. J Allergy Clin Immunol. 2004; 113(4):717–724. Epub 2004/04/22. [PubMed: 15100679]

25. Flood EM, De Cock E, Mork AC, Revicki DA. Evaluating preference weights for the Asthma Symptom Utility Index (ASUI) across countries. Health Qual Life Outcomes. 2006; 4:51. Epub 2006/08/17. [PubMed: 16911790]

26. Zeidler MR, Kleerup EC, Goldin JG, Kim HJ, Truong DA, Simmons MD, et al. Montelukast improves regional air-trapping due to small airways obstruction in asthma. Eur Respir J. 2006; 27(2):307–315. Epub 2006/02/03. [PubMed: 16452585]

27. Yawn BP, Brenneman SK, Allen-Ramey FC, Cabana MD, Markson LE. Assessment of asthma severity and asthma control in children. Pediatrics. 2006; 118(1):322–329. Epub 2006/07/05. [PubMed: 16818581]

28. Tamaoki J, Isono K, Taira M, Tagaya E, Nakata J, Kawatani K, et al. Role of regular treatment with inhaled corticosteroid or leukotriene receptor antagonist in mild intermittent asthma. Allergy Asthma Proc. 2008; 29(2):189–196. Epub 2008/04/24. [PubMed: 18430318]

29. Smith LJ, Holbrook JT, Wise R, Blumenthal M, Dozor AJ, Mastronarde J, et al. Dietary intake of soy genistein is associated with lung function in patients with asthma. J Asthma. 2004; 41(8):11. Epub 2005/01/12.

30. Shih YC, Mauskopf J, Borker R. A cost-effectiveness analysis of first-line controller therapies for persistent asthma. Pharmacoeconomics. 2007; 25(7):577–590. Epub 2007/07/06. [PubMed: 17610338]

31. Sharek PJ, Mayer ML, Loewy L, Robinson TN, Shames RS, Umetsu DT, et al. Agreement among measures of asthma status: a prospective study of low-income children with moderate to severe asthma. Pediatrics. 2002; 110(4):797–804. Epub 2002/10/03. [PubMed: 12359798]

32. Nogueira-Silva L, Martins SV, Cruz-Correia R, Azevedo LF, Morais-Almeida M, Bugalho-Almeida A, et al. Control of allergic rhinitis and asthma test--a formal approach to the development of a measuring tool. Respir Res. 2009; 10:52. Epub 2009/06/19. [PubMed: 19534774]

33. Mougey EB, Feng H, Castro M, Irvin CG, Lima JJ. Absorption of montelukast is transporter mediated: a common variant of OATP2B1 is associated with reduced plasma concentrations and poor response. Pharmacogenet Genomics. 2009; 19(2):129–138. Epub 2009/01/20. [PubMed: 19151602]

34. McKenzie L, Cairns J, Osman L. Symptom-based outcome measures for asthma: the use of discrete choice methods to assess patient preferences. Health Policy. 2001; 57(3):193–204. Epub 2001/07/19. [PubMed: 11459626]

35. Lima JJ, Holbrook JT, Wang J, Sylvester JE, Blake KV, Blumenthal MN, et al. The C523A beta2 adrenergic receptor polymorphism associates with markers of asthma severity in African Americans. J Asthma. 2006; 43(3):7. Epub 2006/06/07.

36. Dixon AE, Kaminsky DA, Holbrook JT, Wise RA, Shade DM, Irvin CG. Allergic rhinitis and sinusitis in asthma: differential effects on symptoms and pulmonary function. Chest. 2006; 130(2):429–435. Epub 2006/08/31. [PubMed: 16899841]

37. 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]

38. 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]

39. Dixon AE, Shade DM, Cohen RI, Skloot GS, Holbrook JT, Smith LJ, et al. Effect of obesity on clinical presentation and response to treatment in asthma. J Asthma. 2006; 43(7):6. Epub 2006/08/11.

40. Reznik M, Sharif I, Ozuah PO. Classifying asthma severity: prospective symptom diary or retrospective symptom recall? J Adolesc Health. 2005; 36(6):537–538. Epub 2005/05/20. [PubMed: 15901521]

41. 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]

42. Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient noncompliance with paper diaries. BMJ. 2002; 324(7347):1193–1194. Epub 2002/05/23. [PubMed: 12016186]

43. Reddel HK, Toelle BG, Marks GB, Ware SI, Jenkins CR, Woolcock AJ. Analysis of adherence to peak flow monitoring when recording of data is electronic. BMJ. 2002; 324(7330):146–147. Epub 2002/01/19. [PubMed: 11799031]

44. Juniper EF, O'Byrne PM, Ferrie PJ, King DR, Roberts JN. Measuring asthma control. Clinic questionnaire or daily diary? Am J Respir Crit Care Med. 2000; 162(4 Pt 1):1330–1334. Epub 2000/10/13. [PubMed: 11029340]

45. Johnston SL, Blasi F, Black PN, Martin RJ, Farrell DJ, Nieman RB. The effect of telithromycin in acute exacerbations of asthma. N Engl J Med. 2006; 354(15):1589–1600. Epub 2006/04/14. [PubMed: 16611950]

46. Cox G, Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, et al. Asthma control during the year after bronchial thermoplasty. N Engl J Med. 2007; 356(13):1327–1337. Epub 2007/03/30. [PubMed: 17392302]

47. 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]

48. Covar RA, Szefler SJ, Zeiger RS, Sorkness CA, Moss M, Mauger DT, et al. Factors associated with asthma exacerbations during a long-term clinical trial of controller medications in children. J Allergy Clin Immunol. 2008; 122(4):741–747. e4. Epub 2008/11/19. [PubMed: 19014765]

49. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R 3rd, 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]

50. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999; 14(4):902–907. Epub 1999/11/26. [PubMed: 10573240]

51. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004; 113(1): 59–65. Epub 2004/01/10. [PubMed: 14713908]

52. Wildfire. Forthcoming 2012 [to be fleshed out].

TABLE I

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

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

ASUI, Asthma Symptom Utility Index; *NIH*, National Institutes of Health; *PACD*, Pediatric Asthma Caregiver Diary; *PASDS*, Pediatric Asthma Symptom Diary Scale.

[*] 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

Methods for measuring and reporting asthma symptoms

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

ASUI, Asthma Symptom Utility Index; *MCID*, minimal clinically important difference; *PACD*, Pediatric Asthma Caregiver Diary; *SABA*, short-acting β-agonist; *UC*, urgent care.

TABLE III

Key points and recommendations

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

TABLE IV

Key articles on validated instruments for measuring asthma symptoms

Key article with validated instrument	Number of citations	Number of full-text reviews
Symptom diary		
Santanello NC, Barber BL, Reiss TF, Friedman BS, Juniper EF, Zhang J. Measurement characteristics of two asthma symptom diary scales for use in clinical trials. Eur Respir J. 1997 Mar;10(3):646-51.	79	45
Santanello NC, Davies G, Galant SP, Pedinoff A, Sveum R, Seltzer J, et al. Validation of an asthma symptom diary for interventional studies. Arch Dis Child. 1999 May;80(5):414-20.	58	18
Santanello NC, Demuro-Mercon C, Davies G, Ostrom N, Noonan M, Rooklin A, et al. Validation of a pediatric asthma caregiver diary. J Allergy Clin Immunol. 2000 Nov;106(5):861-6.	20	10
Symptom questionnaire		
Revicki DA, Leidy NK, Brennan-Diemer F, Sorensen S, Togias A. Integrating patient preferences into health outcomes assessment: the multiattribute Asthma Symptom Utility Index. Chest. 1998 Oct;114(4):998-1007.	80	21
Total	237	94

TABLE V

Validated instruments for measuring symptoms of asthma

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

ASUI, Asthma Symptom Utility Index; *PACD*, Pediatric Asthma Caregiver Diary; *PASDS*, Pediatric Asthma Symptom Diary Scale.

TABLE VI

Longitudinal construct validity

Diary type	Clinical Trial A (n = 239)			Clinical Trial B (n = 104)		
	FEV$_1$	PEFR	SABA inhaler puffs	FEV1	PEFR	SABA inhaler puffs
Daytime scale	−0.28 (−0.39 to −0.16)	−0.49 (−0.58 to −0.38)	0.64 (0.56 to 0.71)	−0.25 (−0.42 to −0.06)	−0.38 (−0.53 to −0.20)	0.58 (−0.43 to 0.47)
Nocturnal scale	−0.38 (−0.48 to −0.26)	−0.32 (−0.43 to −0.20)	0.48 (0.37 to 0.57)	−0.28 (−0.45 to −0.09)	−0.51 (−0.64 to −0.35)	0.47 (0.30 to 0.61)

Pearson correlation coefficients (95% CI)

CI, confidence interval; *FEV$_1$*, forced expiratory volume in 1 second; *PERF*, peak expiratory flow rate; *SABA*, short-acting β-agonist.