THE ASTHMA SYMPTOM UTILITY INDEX: RELIABILITY, VALIDITY, AND RESPONSIVENESS AMONG ADULT ASTHMA PATIENTS

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ABSTRACT

THE ASTHMA SYMPTOM UTILITY INDEX: RELIABILITY, VALIDITY, AND RESPONSIVENESS AMONG ADULT ASTHMA PATIENTS

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Patient reported outcome (PRO) instruments are frequently used to assess effectiveness of asthma therapy in clinical research and clinical practice. Several instruments exist for assessing asthma control and asthma-related quality of life. We used the Asthma Symptom Utility Index (ASUI), an instrument designed to assess asthma symptoms, as an example to demonstrate the methodology for evaluating the psychometric properties of PRO instruments. The ASUI is a 10-item instrument developed to measure the frequency and impact of asthma symptoms over a two week recall period. In two groups of adult asthma patients participating in large multicenter randomized trials, we showed that the ASUI has good construct validity as demonstrated by significant correlations between ASUI scores and Asthma Control Questionnaire (ACQ) scores (Spearman correlation r = -0.79, 95% CI [-0.85, -0.75], P<0.001) and Mini Asthma Quality of Life Questionnaire (Mini AQLQ) scores (r = 0.59, 95% CI [0.51, 0.61], P<0.001). The ASUI also showed robust internal consistency reliability of 0.74 (Cronbach's alpha), test-retest reliability 0.76 (intra-class correlation), as well as responsiveness to change.

To my lovely wife Philomina and our daughters – Megan, Mariah, Melanie and Michelle

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ABBREVIATIONS

ABP Asthma Bother Profile

ACT Asthma Control Test

ACQ Asthma Control Questionnaire

AIS Asthma Impact Survey

ALA-ACRC American Lung Association-Asthma Clinical Research Centers

ANOVA Analysis of Variance

AQLQ Asthma Quality of Life Questionnaire

AQLQ-S Asthma Quality of Life Questionnaire-Standardized

ASF Asthma Short Form

ASUI Asthma Symptom Utility Index

c-ACT Childhood Asthma Control Test

CHSA Child Health Survey for Asthma

CHSA-C Child Health Survey for Asthma –child version

COPD Chronic Obstructive Pulmonary Disease

EPAC Episodes of Poor Asthma Control

FEV1 Forced Expiratory Volume in One second

GINA Global Initiative for Asthma

ICC Intraclass correlation

M-AQLQ Marks – Modified Asthma Quality of Life

MID Minimal Important Difference

Mini-AQLQ Mini-Asthma Quality of Life Questionnaire

NAEPP National Asthma Education and Prevention Program

NIH National Institutes of Health

PACD Pediatric Asthma Caregiver Diary

PACQLQ Pediatric Asthma Caregiver Quality of Life Questionnaire

PAQLQ Pediatric Asthma Quality of Life Questionnaire

PASDS Electronic Pediatric Asthma Symptom Diary Scale

PedsQL 3.0 Asthma Module Pediatric Quality of Life Inventory 3.0 Asthma Module

PEF Peak Expiratory Flow Rate

Pictorial PAQLQ Pictorial Quality of Life Measure for Young children with Asthma

PPI proton pump inhibitors

PRO Patient reported Outcome

RR Relative Risk

SARA Study of Acid Reflux and Asthma

SD Standard Deviation

SEM Standard Error of Measurement

SIIVA Safety of Inactivated Influenza Vaccine in Asthma

VAS Visual Analog Scale

INTRODUCTION

Outcome measures in asthma clinical research and routine clinical care include objective measures such as lung function[1], biomarkers of airway inflammation[2], asthma exacerbations[3], and health care utilization and costs[4]. However, these objective measures may correlate poorly with the patients' perception of asthma control in terms of symptoms and impact on their quality of life[5, 6]. Recent international guidelines for the assessment and monitoring of asthma have defined the concepts of asthma severity and asthma control[7-9]. Asthma severity is an inherent trait of the patient that reflects the intrinsic intensity of the disease process and is more or less constant[9]. Asthma control is the extent to which manifestations of the disease are reduced or removed by therapy[9]. Two domains of asthma control are identified in the guidelines: current impairment and future risk. Current impairment includes the extent of asthma symptoms, the amount of activity limitation, and asthma-related quality of life[9]. The risk domain of asthma control is defined by the presence of adverse outcomes such as exacerbations, accelerated decline in lung function, or treatment-related side effects[9]. The clinical manifestations of asthma have wide patient variability in frequency and intensity[8, 9] and no single asthma symptom is ideal for the comprehensive assessment of asthma control. Asthma questionnaires that group several individual asthma manifestations to provide a composite score are thus essential. Patient-reported

outcomes (PRO) are questionnaires that provide a report of a patient's health condition, directly from the patient and without any interpretation of the response by a clinician[7]. It has been recommended in international asthma management guidelines that PROs be used to assess the effectiveness of asthma therapy in clinical research and clinical practice[8, 9].

Several PRO instruments currently exist for use in assessing asthma outcomes in clinical research. Unfortunately, there is a lack of outcome standardization in asthma clinical research making it difficult to examine and compare asthma outcomes across clinical studies. In March, 2010, a consortium of several National Institutes of Health (NIH) institutes, and the Agency for Healthcare Research and Quality convened an Asthma Outcomes workshop in Bethesda, MD to establish standard definitions and data collection methodologies for validated PRO instruments in asthma clinical research and also to identify promising outcome measures for use in asthma clinical research[10]. Three types of PRO instruments were identified - composite scores of asthma control, asthma-related quality of life, and asthma symptoms[10]. The NIH workshop further defined the outcome measures as core outcomes, supplemental outcomes, or emerging outcomes based on the degree of standardization and validation[10]. Core asthma outcome measures are well standardized, well validated, and include the most important clinical aspects of asthma[10]. These are considered as required outcome measures in the funding of NIH-initiated asthma clinical trials and large observational studies[10]. Supplemental asthma outcome measures are also well standardized and

somewhat well validated but inclusion in funded research is not mandatory[10]. Emerging asthma outcome measures are those that are not yet well standardized and still require further development and validation[10]. The workshop recommended that core instruments be identified for each of the three domains - composite scores of asthma control, asthma-related quality of life, and asthma symptoms[10]. The Asthma Symptom Utility Index (ASUI) was identified as a supplemental outcome measure for assessing asthma symptoms.

In the first part of this dissertation, we present a summary of some PRO instruments currently available for use in asthma clinical research. Next, we briefly describe the criteria for evaluating the psychometric properties of PRO instruments. Finally, we use the ASUI as an example to demonstrate the methodology for evaluating the psychometric properties of an instrument.

CHAPTER 1

PATIENT REPORTED OUTCOME MEASURES IN ASTHMA CLINICAL RESEARCH

Typical asthma manifestations such as cough, wheeze, dyspnea, activity limitation, nocturnal awakening, and airway obstruction are characterized by marked intra-patient and inter-patient variability. Consequently, they require frequent monitoring to document their occurrence and to assess their impact on patients. In asthma research, the methodical assessment of asthma symptoms, overall asthma control, and asthma-related quality-of-life is best achieved with standardized instruments, such as asthma diaries or asthma questionnaires.

Composite scores of asthma control

Retrospective questionnaires for assessing asthma control usually combine several individual asthma related variables to generate a composite score[11, 12]. The goal is to reflect the degree to which all manifestations of asthma disease are seen by the patient as globally controlled by therapy. These manifestations include asthma symptoms, the amount of activity limitation, asthma-related quality of life, and lung function as measured by the peak expiratory flow rate (PEF) or the forced expiratory volume in the first second (FEV1) [9, 12]. In developing questionnaires to assess asthma control, the choice of items is generally based on expert opinion, focus group discussions, or both[11, 12]. Overall, there is no consensus regarding which specific items

should be included in questionnaires for assessing asthma control[11, 12]. The Asthma Control Questionnaire (ACQ) [12] and the Asthma Control Test (ACT) [11] are well standardized, well validated, and have been extensively used in asthma clinical research for assessing asthma control in adults. Both questionnaires are recommended by the NIH workshop as core outcome instruments for measuring asthma control[13]. The Childhood Asthma Control Test (c-ACT) [14] is well validated in children aged 6-16 years and is also recommended as a core asthma outcome instrument in the pediatric population[13]. A list of some currently available questionnaires for assessing asthma control is presented on Table 1.

Asthma-related quality of life

The burden of asthma as measured by other objective methods does not always correlate with the patient's perception of the impact of asthma on their quality of life[5, 6]. Asthma-related quality of life questionnaires are intended to assess the perceived impact of asthma on the patient's daily activities[15]. They also assess the patient's perspective on the overall effectiveness of asthma disease management[15]. Unfortunately, a majority of the currently available asthma-related quality of life instruments include many items that relate more to the domain of impairment (health status, functional status, emotional and social occupational functioning etc.) as opposed to how much such impairment matters to the patient[16-20]. Some currently available

asthma quality of life questionnaires are presented on Table 1. Many of these questionnaires have not been extensively validated among low-income, low literacy, or minority populations that are disproportionately affected by the burden of asthma[15]. In light of these limitations, the NIH workshop does not recommend any particular asthma-related quality of life instrument as a core outcome measure[15]. Many of the validated asthma-related quality of life instruments are recommended as supplemental outcome measures in asthma clinical research[15].

Table 1: Questionnaires for assessing asthma control and asthma-specific quality of life in adults and children

Adult asthma control questionnaires	Pediatric asthma control questionnaires
¶ACT- Asthma Control Test[11]	¶c-ACT – Childhood Asthma Control Test[14]
¶ACQ – Asthma Control Questionnaire[12]	¶ACQ – Asthma Control Questionnaire[53]
¥ATAQ – Asthma Therapy Assessment Questionnaire[53]	¥c-ATAQ – ATAQ for Children and Adolescents[54]
¥ACSS – Asthma Control Scoring System	¥CAN – Asthma Control in Children
¥PCAQ – Perceived Control of Asthma Questionnaire	¥Breathmobile – Breathmobile Assessment of Asthma Control
¥SASCQ – Seattle Asthma Severity and Control Questionnaire	¥PACT – Pediatric Asthma Control Tool
¥ACCI – Asthma Control and Communication Instrument	¥TRACK – Test for Respiratory and Asthma Control in Kids

Table 1 (cont'd).

Adult asthma quality of life questionnaires	Pediatric asthma quality of life questionnaires
¥ABP- Asthma Bother Profile[21]	¥CHSA – Child Health Survey for Asthma[22]
¥AIS – Asthma Impact Survey[23]	§§CHSA-C – Child version[22]
¥AQLQ-S – Asthma Quality of Life Questionnaire[16, 24]	¥PAQLQ – Pediatric Asthma Quality of Life Questionnaire[18]
¥Mini-AQLQ – Mini-Asthma Quality of Life Questionnaire[19]	¥PACQLQ – Pediatric Asthma Caregiver Quality of Life Questionnaire[17]
¥LWAQ – Living With Asthma Questionnaire[25]	§§Pictorial PAQLQ - Pictorial Quality of Life Measure for Young children with Asthma[26]
¥M-AQLQ-Marks – Modified Asthma Quality of Life[20]	¥PedsQL 3.0 Asthma Module – Pediatric Quality of Life Inventory 3.0 Asthma Module[27]
¥ASF - Asthma Short Form[28]	

¶ - *Recommended by the NIH workshop as a core instrument*[15]

§§ - Recommended by NIH workshop as emerging instrument[15]

¥ - Recommended by NIH workshop as supplementary instrument[15]

Asthma symptoms

The diagnosis of asthma in clinical practice is usually suggested by typical symptoms such as cough, chest tightness, dyspnea, wheeze, nocturnal awakening, and activity limitation. Asthma symptoms have considerable variability in frequency and intensity. Asthma symptoms can be recorded prospectively over a defined period of time (asthma diaries), or with the use of retrospective questionnaires completed during clinic or research visits. Prospectively recorded symptoms are often reported in asthma clinical research as symptom-days, symptom-free days, and number of symptom-days per week or as a summary score[30-33]. Retrospective questionnaires for asthma symptoms usually report a summary score[34]. However, unlike asthma control questionnaires which focus on the overall patient assessment of how their asthma disease is controlled, symptom questionnaires measure the severity and frequency of specific asthma symptoms.

Asthma diaries

In addition to information about asthma symptoms, diaries also include questions that inform about the occurrence of major asthma-related events such as exacerbations or loss of control (use of systemic corticosteroids for asthma, an unscheduled contact with a healthcare provider for asthma). A daily measure of lung function such as PEF and FEV1 is often included in asthma diaries as well[30]. Asthma diaries have the advantage of not being limited by patient recall. Also, information about major asthma-

related events are recorded and monitored in real time with an opportunity for timely intervention. The main concerns with paper diaries include incorrect data, incomplete or missing data, and fabricated data. Use of telephone-administered diaries, online diaries, or handheld electronic diaries can potentially mitigate some of these concerns. The Daytime Symptom Diary Scale and Nocturnal Diary Scale (daily diary) [33] is a recommended supplemental outcome measure for use in adult asthma patients[29]. The Pediatric Asthma Caregiver Diary (PACD) [32] is recommended as a supplemental outcome instrument in children aged 2 to 5 years old[29]. Another diary, the Electronic Pediatric Asthma Symptom Diary Scale (PASDS) [31] is recommended by the NIH workshop as an emerging outcome measure in children aged 6 to 14 years old[29]. Despite the availability of these diaries, many asthma researchers tend to use customized asthma diaries based on their specific research needs.

Retrospective asthma symptom questionnaires

The Asthma Symptom Utility Index (ASUI) [34] is the only available standardized retrospective questionnaire for asthma symptoms. It is a 10-item questionnaire designed to assess the frequency and severity of four asthma symptoms (cough, wheeze, dyspnea, and nocturnal awakening), as well as side effects from asthma medications over a two week recall period. The items are weighted according to patient preferences and the scoring is done using a calculation based on a previously derived formula[34]. The details on how the ASUI was developed and how the multiattribute

utility function was derived are provided in the appendix. The summary score of the ASUI is a continuous scale from 0 to 1 with lower scores indicating worse asthma symptoms.

The ASUI is a good alternative in cases where researchers do not want to use daily asthma symptom diaries. Even though some items on the ASUI may overlap with items on other asthma control and asthma quality of life questionnaires[16, 19, 20], composite scores obtained from these other instruments allocate the same weight to all items even though some symptoms may be more troublesome to patients than others. By integrating the patient's preference for specific symptom states, the ASUI is ideal for use in cost utility analyses. The ASUI has emerged as the major asthma symptom scale in multiple clinical trials[35-37]. However, it was not recommended by the NIH workshop as a core asthma outcome measure because of limited characterization of the psychometric properties[29].

CHAPTER 2

CRITERIA FOR EVALUATING THE PSYCHOMETRIC PROPERTIES OF PATIENT REPORTED OUTCOME INSTRUMENTS

The methodology for evaluating a PRO instrument includes an assessment of its validity, reliability, and responsiveness[15, 38-40].

Validity

The validity of a PRO instrument is the degree to which it actually measures what it purports to measure[15, 39, 40]. Several dimensions of validity can be assessed including: content validity, face validity, construct validity, criterion validity, and predictive validity. In the context of asthma, content validity is the extent to which all the components of the measured domain - asthma control, or asthma-related quality of life, or asthma symptoms - are comprehensively sampled by the items in the questionnaire, as determined by a panel of experts[15].

Face validity refers to the subjective determination by an expert panel that the items included in the instrument seem appropriate and relevant[15]. There is no quantitative measurement for face validity.

Construct validity evaluates whether the instrument correlates with other instruments that measure the same domain or other domains of the disease in a predictable manner[15]. When the outcome measures are a continuous scale, as is the case with the ASUI, construct validity is calculated using Pearson's or Spearman's

correlation coefficients[15]. Pearson's correlation is best used for interval data that has a normal distribution. Pearson's correlation between instruments A and B for a population sample with sample size n is derived from the following equation:

$$r_{xy} = \frac{n\sum XY - \sum X \sum Y}{\sqrt{[n\sum X^2 - (\sum X)^2] * [n\sum Y^2 - (\sum Y)^2]}}$$

Where X denotes values obtained from instrument A, and Y denotes the values obtained from instrument B at the same point in time. Nominal data of ordinal data such as data derived from most PRO instruments in asthma are nonparametric and therefore the Spearman's rank correlation is the more appropriate method for determining correlation between results obtained from two instruments. Consider two instruments A and B with results on an ordinal scale, administered at the same time to n subjects. The Spearman's rank correlation between instruments A and B will be determined by the following equation:

$$\rho = \frac{\sum_i (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_i (x_i - \bar{x})^2 \sum_i (y_i - \bar{y})^2}}$$

Where i = paired score. The raw values X_i, and Y_i, are converted to ranks x_i, and y_i. In the current PRO literature, there is no defined level of correlation that is accepted as the standard to define good construct validity. In general, most reports use a correlation of greater than 0.5 to indicate good construct validity[11-14]. Construct validity is also referred to as convergent validity, known-groups validity, or discriminant validity[15, 23, 41].

Criterion validity is the degree of correlation of an instrument with the "gold standard" outcome measure and is measured by Pearson's or Spearman's correlation coefficients[12, 19, 42].

Predictive validity is the ability of different pre-specified levels of an instrument to predict the occurrence of a subsequent event, such as an asthma exacerbation, during a defined period of time[41]. This is determined by first grouping the sample into different levels and then calculating the relative risk or the odds of an outcome such as an exacerbation.

Reliability

Reliability of a PRO instrument refers the degree to which it is free from random measurement error[39, 40]. According to the reliability theory, the variance of scores obtained from an instrument (σ^2_X) is the sum of the variance of true scores (σ^2_T) plus the variance of errors of measurement (σ^2_E).

$$\sigma^2_X = \sigma^2_T + \sigma^2_E.$$

If we assume that the variation in scores is due only to variability in true scores and variability in errors of measurement. The reliability coefficient is therefore defined as the ratio of the true variance to the total variance:

$$\rho = \sigma^2_T / \sigma^2_X.$$

Or alternatively

$$\rho = 1 - \sigma^2_E / \sigma^2_X.$$

In practice, there is no way to observe or directly calculate the true score. The two methods that have been frequently used to estimate the reliability of PRO instruments are internal consistency reliability and test-retest reliability[39, 40].

Internal consistency reliability is a measure that is based on the correlations between different items on the same questionnaire[40]. It therefore assesses the extent to which the individual items on the questionnaire measure the same construct[40]. The Cronbach's alpha statistic is generally used as a measure of internal consistency [39, 40]. To calculate the Cronbach's alpha coefficient (α), let σ^2_X be the variance of the observed total test scores and let σ^2_{Yi} be the variance of component *i* for the current sample of persons. The Cronbach's alpha coefficient is therefore defined by;

$$\alpha = \frac{K}{K-1}\left(1 - \frac{\sum_{i=1}^{K} \sigma^2_{Y_i}}{\sigma^2_X}\right).$$

Where K is the number of components (*K-items*). Values of Cronbach's alpha above 0.70 are generally accepted to indicate a good internal consistency for an instrument[39].

Test-re-test reliability or reproducibility measures the variation in measurements taken by the instrument during periods when the participants are assumed to have remained stable[39]. The intraclass correlation coefficient (ICC = $\rho = \sigma^2_T / \sigma^2_X$) for continuous data and the Kappa coefficient (**K**) for categorical data are used to assess test-retest reliability[39]. Test-retest reliability values of at least 0.70 are considered

minimally acceptable for the purpose of assessing the psychometric properties of PRO measures[39].

Responsiveness

Responsiveness refers to the ability of an instrument to detect clinically important changes in the disease over a time period during which change is expected to have occurred[15, 40]. Responsiveness is a measure of the longitudinal validity of the instrument. It is calculated by determining the extent to which changes in questionnaire scores correlate with changes in other measures of the same construct in the hypothesized direction over a defined period of time[40]. In addition to determining that there is a statistically significant correlation in terms of questionnaire scores with other measures, there is need to determine a minimal level of change in the score on the instrument that is consistent with a real benefit or worsening.

CHAPTER 3

THE PSYCHOMETRIC PROPERTIES OF THE ASTHMA SYMPTOM UTILITY INDEX (ASUI): METHODS AND RESULTS

The ASUI was developed in 1998 by Revicki et al. to measure the degree of asthma symptoms and their impact on patients[34]. It is a 10-item questionnaire designed to assess the frequency and severity of four asthma symptoms (cough, wheeze, dyspnea, and nocturnal awakening), as well as side effects from asthma medications over a two week recall period. The items are weighted according to patient preferences and scored based on a previously derived formula[34]. The summary score of the ASUI is a continuous scale from 0 to 1 with lower scores indicating worse asthma symptoms.

The initial study by Revicki et al. showed that the ASUI had good reproducibility (intraclass correlation [ICC] = 0.74), good construct validity (Pearson's correlation coefficient with the AQLQ = 0.77), and good discriminant validity[34]. Test-retest reliability, predictive validity, and responsiveness to change have not been previously determined. In addition, a minimal important difference (MID) for the ASUI is not yet established. Our objective was to assess the reliability, validity, and responsiveness to change of the ASUI in a population of adult asthma patients participating in two multicenter randomized trials.

Methods

Data collection

Patients

Data from 1648 adult asthma participants (≥ 18 years) enrolled in two completed clinical trials conducted by the American Lung Association-Asthma Clinical Research Centers (ALA-ACRC) were included in this analysis[36, 43]. The Study of Inactivated Influenza Vaccine in Asthmatics (SIIVA) was a multicenter, randomized, double-blind, placebo-controlled, crossover trial to investigate the safety of the inactivated trivalent split-virus influenza vaccine in 2032 patients with asthma (age range, 3 to 64 years). It was conducted between September 15 and November 30, 2000[43]. The patients were followed for 14 days after injection of either the influenza vaccine or placebo for a total of 28 days of follow-up for each participant. The study showed that the inactivated trivalent split-virus influenza vaccine was safe in adults and children with asthma[43].

The Study of Acid Reflux and Asthma (SARA) trial was a multicenter, randomized, placebo-controlled, double-blind trial conducted between October 2004 and May 2008, to test if six months of proton pump inhibitors (PPIs) (esomeprazole - Nexium, Astra-Zeneca) versus placebo improved asthma control [36]. It showed esomeprazole that did not improve asthma control in adults whose asthma was not well controlled on inhaled corticosteroids[36].

Procedures

The protocols for both studies were approved by institutional review boards in each of the participating centers and informed consent was obtained from each participant. The SARA trial was registered on ClinicalTrials.gov (NCT00069823); the SIIVA trial was conducted before NIH registration requirements were instituted. In the SIIVA trial, baseline demographic data and ASUI score were obtained for all participants (N=1236). Baseline spirometry was obtained in a subset of participants (N=704). After administration of either vaccine or placebo, participants were followed for 14 days during which they kept a daily asthma diary with information on asthma related symptoms, peak expiratory flow rate (PEF), healthcare utilization, and medication use. After crossover, there was another 14 day follow-up period[43]. The primary outcome measure was an exacerbation of asthma. In the SARA trial (N=412), baseline demographic data, spirometry, ASUI score, ACQ score, and the Mini AQLQ score were obtained. Patients were then randomized to either esomeprazole 40mg twice daily or placebo in addition to their inhaled corticosteroid regimen for a total of twenty-four weeks. During follow-up clinic visits that occurred every four weeks, ASUI scores, ACQ scores, and Mini AQLQ scores were obtained. Patients also kept an asthma diary that was returned during each clinic visit[36]. The primary outcome for the SARA trial was the rate of episodes of poor asthma control, as assessed on the basis of entries in asthma diaries[36]. An episode of poor asthma control (EPAC) was defined as the occurrence of any one of the following: 1) peak flow decrease of ≥30% from personal best, 2) increased rescue medication use above the average reported during the two weeks

before randomization, 3) new or increased oral corticosteroids for asthma, 4) an unscheduled use of healthcare for treatment of asthma.

Assessments

Construct validity

Construct validity of the ASUI was assessed using data from the SARA trial by computing Spearman's rank correlations (as described above) between baseline ASUI scores and (1) baseline ACQ scores, and (2) baseline Mini AQLQ scores.

Known-groups validity

Known-groups validity is a form of construct validity that involves categorizing the patients by one method of measurement and then using ANOVA methods to test the significance of differences in mean scores of another measurement method across the previously defined categories. The categories are usually based on a well-known classification scheme for that method of measurement. Known-groups validity was assessed using data from the SIIVA trial by comparing the mean baseline ASUI score across three categories of baseline percent predicted pre-bronchodilator forced expiratory volume in one second (FEV1) values: (1) less than 60%; (2) 60% to 79 %; (3) greater than or equal to 80%. These categories of FEV1 are based on approximate levels of asthma severity by lung function criteria as defined by the National Asthma Education and Prevention Program (NAEPP). The mean baseline ASUI score was also compared across a four point scale of ascending asthma severity among SIIVA

participants based on asthma medication use at baseline (1 = intermittent, 2 = mild, 3 = moderate, 4 = severe) [44]. Previous studies have shown that current asthma medication use complements other classifications of asthma severity[45, 46]. One-way ANOVA was used to test the significance of group differences in mean ASUI scores and the Tukey Honest Significant Difference (HSD) method was used for pairwise comparisons.

Predictive validity

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

Reliability

To evaluate the internal consistency reliability, the Cronbach's α coefficient was calculated using baseline ASUI data from both SIIVA and SARA.

Test-retest reliability was assessed by calculating the intraclass correlation coefficient (ICC) between the baseline ASUI score and the ASUI score at the next follow-up visit (four weeks apart) using data from participants in the SARA trial with stable asthma. Stable asthma was defined by the absence of an episode of poor

asthma control (EPAC) [36], and no clinically significant change in the ACQ scores and Mini AQLQ scores (change less than 0.5 points). An EPAC was defined by the occurrence of at least one of the following events: an increase in rescue medication use for asthma symptoms by four or more inhalations per day over baseline, the occurrence of an unscheduled contact with a healthcare provider for asthma, use of systemic corticosteroids for asthma, or a decrease of 30% or more in morning PEF on 2 consecutive days, as compared with the patient's best PEF during the run-in period[36].

Responsiveness

To determine the responsiveness to change of the ASUI, data from the SARA trial was used. For each participant, there were seven clinic visits each separated by four week intervals from randomization to the end of the study. During each clinic visit, ASUI, ACQ, and Mini AQLQ scores were obtained. All participants were instructed to keep a daily asthma diary that was returned to the clinic during subsequent visits. Linear regression with robust variance estimates and exchangeable correlation structure was used to compare mean changes in ASUI scores across groups of participants who differed by ≥ 10% in percent predicted FEV1 values, and by 0.5 points in ACQ[47]. The participant groups for each measure were derived as follows:

1. Percent predicted FEV1 values: Previous studies have used 10% as the cutoff for significant change in percent predicted FEV1based on findings among the chronic obstructive pulmonary disease (COPD) population [23, 41, 48, 49]. The change in percent predicted FEV1 values was derived by

subtracting the baseline percent predicted FEV1 values from the follow-up percent predicted FEV1 and dividing by the baseline percent predicted value. Participants were categorized as better if the increase in percent predicted FEV1 was greater than or equal to 10%, worse if the percent predicted FEV1 decreased by greater than or equal to 10%, else they were categorized as unchanged. The mean changes in ASUI were then compared between the three groups.

2. ACQ scores: The minimal change in the ACQ score that indicates a clinically important difference to the patient (MID) has been determined to be 0.5 points[12]. Participants were categorized as better if the decrease in their ACQ score was greater than or equal to 0.5, worse if the increase in ACQ score was greater than or equal to 0.5, or unchanged if the change was between -0.5 and +0.5. The mean changes in the ASUI scores were then compared between the three groups: better, same, or worse.

Results

Study populations

A summary of the baseline characteristics of the study participants from the SIIVA and SARA trials is presented in Table 2. Data from 1236 study participants ages 18 years and older were included in the SIIVA trial. The mean age of these asthma patients was 42 years (SD, 12). A majority of them were female (75%), and White (67%). The SARA trial included 412 participants. The mean age of asthma patients in SARA was 41 years (SD, 13). The majority were again female (68%), fifty percent were White, and 38% were Black.

Table 2: Patient characteristics at baseline

Characteristic	**SIIVA** (n=1236)	**SARA** (n= 412)
Age, year (SD)	42 (12)	41 (13)
Female (%)	923 (75)	279 (68)
Race or ethnic group – no. (%)		
White	828 (67)	205 (50)
Black	281 (23)	157 (38)
Hispanic	79 (6)	41 (10)
Other	44 (4)	9 (2)
Asthma questionnaire scores, mean (SD)		
ASUI↑ (0-1)	0.82 (0.18)	0.76 (0.16)
ACQ↓ (0-7)	NA	1.7 (0.9)
Mini AQLQ↑ (1-7)	NA	4.7 (1.2)
*Pulmonary function, mean (SD)**	SIIVA (n=704)	SARA (n= 412)
Pre-bronchodilator FEV1, Liters	2.6 (0.9)	2.4 (0.7)
Pre-bronchodilator FEV1, % predicted	83.4 (21)	76.7 (15)

**Pulmonary function available for 704 (57%) SIIVA participants*
ASUI: Asthma Symptom Utility Index. Scores on the ASUI range from 0 to 1, with higher scores indicating less severe asthma symptoms
ACQ : Asthma Control Questionnaire. Scores on the ACQ range from 0 to 7, with lower scores indicating better asthma control and 0.5 as the minimal clinically important difference. Mini AQLQ : Mini Asthma Quality of Life Questionnaire. Scores on the Mini AQLQ range from 1 to 7, with higher scores indicating better quality of life and 0.5 as the minimal clinically important difference. FEV1: forced expiratory volume in 1 second and the predicted values are from Hankinson et al.[50] SARA: Study of Acid Reflux and Asthma. SIIVA: Safety of Inactivated Influenza Vaccine in Asthma

Construct validity of the ASUI

Statistically significant Spearman's correlations were observed between baseline ASUI scores and baseline ACQ scores ($r = -0.79$, $P < 0.001$), and baseline Mini AQLQ scores ($r = 0.59$, $P < 0.001$). The negative correlation with the ACQ is due the fact that unlike the ASUI, lower scores in the ACQ indicate good asthma control.

Known-groups validity

The F statistics from the overall one-way ANOVA tests were significant indicating that one group differed significantly from another. We then proceeded with pairwise comparisons using the Tukey Honest Significant Difference (HSD) method. The difference in mean ASUI scores between patients with poor baseline lung function (percent predicted FEV1 <60%) and those with good baseline lung function (percent predicted FEV1 ≥ 80%) was statistically significant (0.76 vs. 0.85, $P < 0.0001$) [Tables 3 and 4]. This a positive linear relationship between the mean ASUI score and category of percent predicted FEV1 is also demonstrated in Figure 1. The difference in mean ASUI scores between patients with severe asthma and those with intermittent asthma was statistically significant (0.71 vs. 0.85, $P < 0.0001$) [Tables 3 and 4]. This negative linear relationship between mean ASUI score and asthma severity based on asthma medication use at baseline is also demonstrated in Figure 2.

Table 3: Known-groups validity tests on mean ASUI scores at baseline [SIIVA trial]

	Number of participants (N)	Mean (SD) ASUI score	F statistic/P-value
Percent predicted FEV1			12.5/<0.0001
≥ 80%	405	0.85 (0.15)	
60% to 79%	188	0.81 (0.17)	
< 60%	97	0.85 (0.18)	
Asthma severity based on baseline medication use			25.4/<0.0001
Intermittent	332	0.85 (0.14)	
Mild	453	0.83 (0.16)	
Moderate	298	0.80 (0.19)	
Severe	137	0.71 (0.20)	

ASUI: Asthma Symptom Utility Index, SIIVA: Safety of Inactivated Influenza Vaccine In Asthma, FEV1: Forced expiratory volume in the first second and the predicted values are from Hankinson et al.[50]

Table 4: Pairwise comparison of differences in mean ASUI score by categories of lung function and asthma severity [SIIVA trial]

Predicted Comparison	Difference in mean ASUI score	95%CI		P-value
Percent predicted FEV1				
FEV1 <60% vs. FEV1 ≥ 80%	-0.09	-0.13	-0.06	0.03
FEV1 <60% vs. 60% ≤ FEV1 ≤79%	-0.05	-0.09	-0.007	0.06
Asthma severity based on baseline medication use				
Intermittent vs. Severe	-0.14	-0.19	-0.10	0.02
Intermittent vs. moderate	-0.06	-0.09	-0.02	0.08
Mild vs. Severe	-0.12	-0.16	-0.08	0.02
Moderate vs. Severe	-0.09	-0.13	-0.04	0.03

Pairwise comparisons of means were obtained using the Tukey Honest Significant Difference (HSD) method with difference in mean ASUI score the 95%CI reported.

Figure 1. Mean of ASUI with Standard Error by Categories of Percent Predicted FEV1

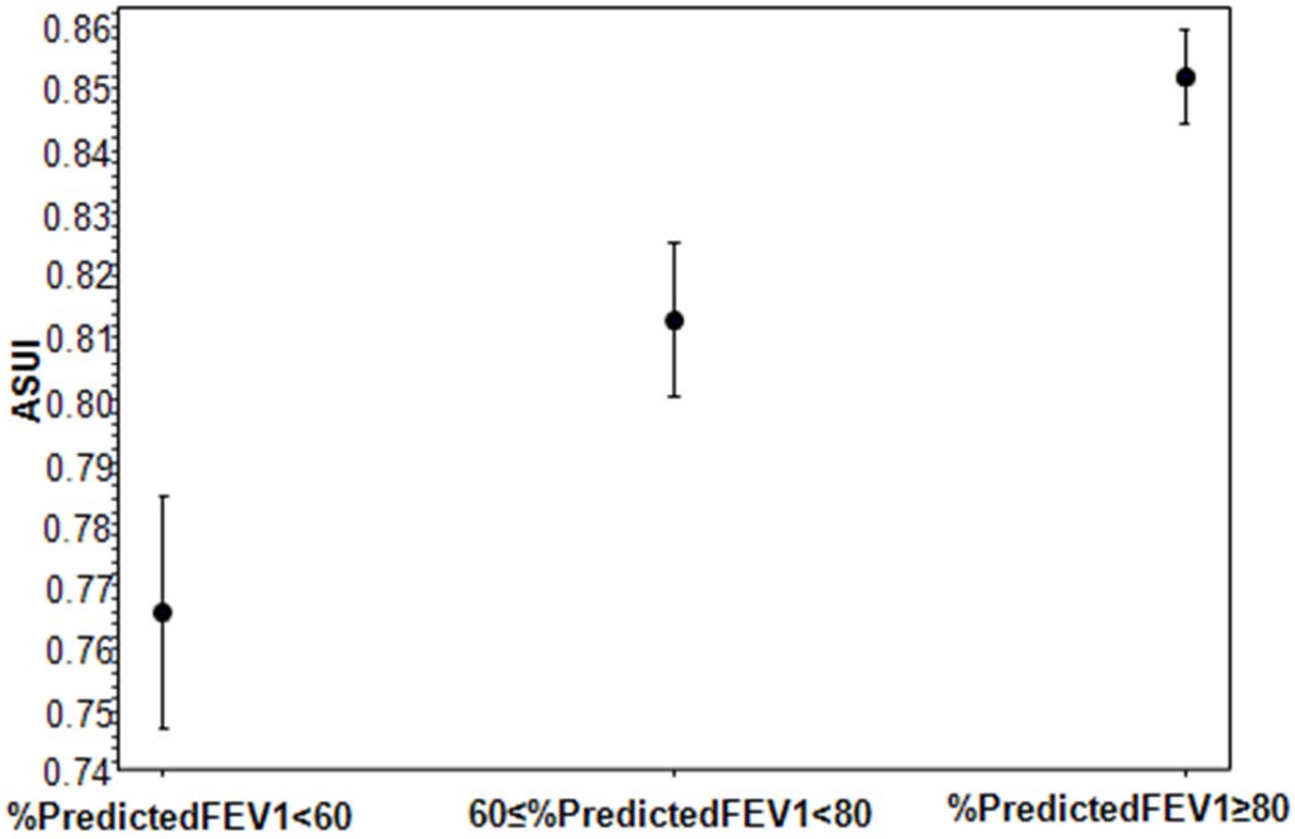
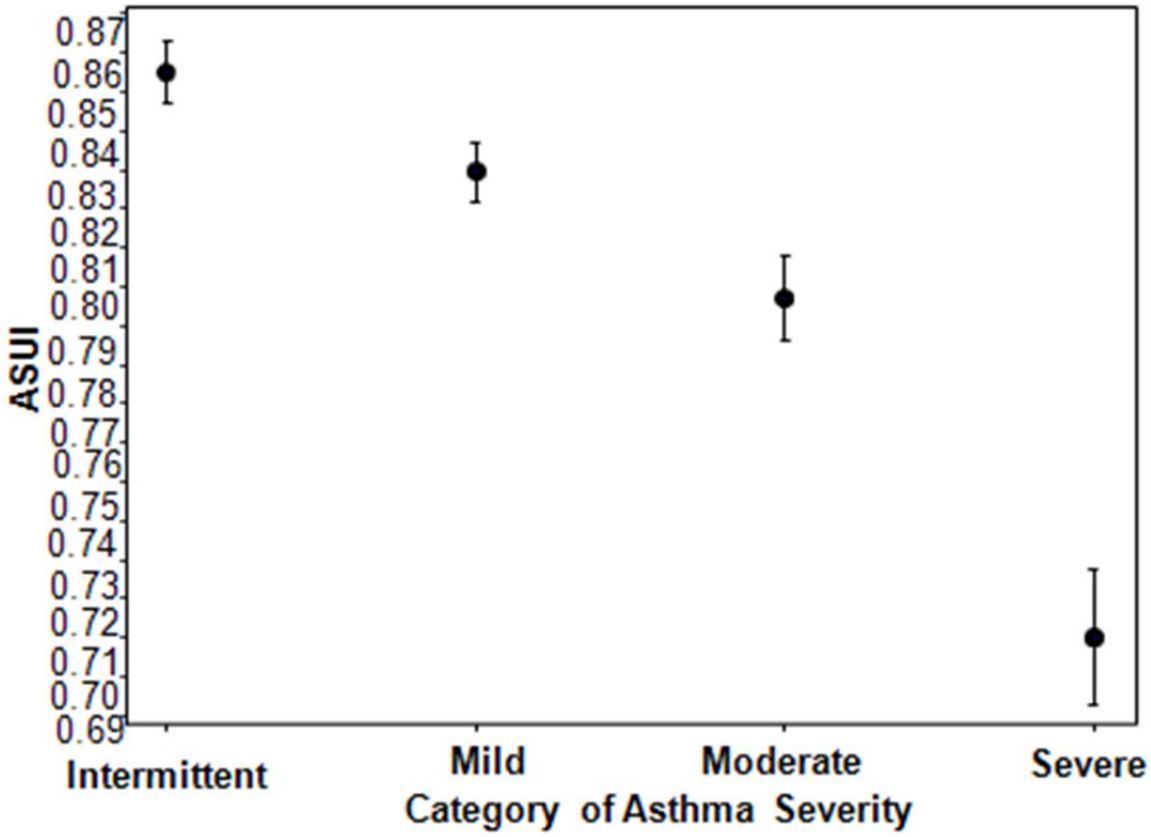


Figure 2. Mean of ASUI with Standard Error by Category of Asthma Severity



Predictive validity of the ASUI

In the SIIVA data, an episode of poor asthma control (EPAC) was defined as the occurrence of any one of the following: 1) peak flow decrease of ≥30% from personal best, 2) increased rescue medication use above the average reported during the two weeks before randomization, 3) new or increased oral corticosteroids for asthma, 4) an unscheduled use of healthcare for treatment of asthma. The frequency of EPACs ranged from 13% in the highest quartile of ASUI to 39% in the lowest quartile of ASUI (table 5). Compared to patients in the highest quartile of baseline ASUI (score >0.95), SIIVA participants with a baseline ASUI score of ≤ 0.73 (lowest quartile) were 1.44 times more likely to experience an EPAC over the next two weeks (Table 5). There was a dose response relationship with increasing likelihood of an EPAC by decreasing quartile of baseline ASUI score (Table 5). The overall frequency of asthma exacerbations as defined by new or increased oral corticosteroid use or an unscheduled healthcare contact for asthma, was low (4-11%) across all four groups. Participants in the lowest quartile were 8% more likely to experience an exacerbation compared to those in the highest quartile (Table 5).

Table 5: Predictive validity of the ASUI: relationship to frequency of EPACs and exacerbations. [SIIVA trial]

	EPACS*		Exacerbations**	
Quartiles of ASUI	**Frequency (%)**	**Relative risk (RR) (95%CI)**	**Frequency (%)**	**Relative risk (RR) (95% CI)**
>0.95 (n=321)	13	Reference = 1	4	Reference = 1
0.87 to 0.95 (n= 263)	24	1.13 (1.05-1.23)	4	1.00 (0.96-1.03)
0.74 to 0.86 (n= 290)	30	1.24 (1.13-1.35)	7	1.03 (0.99-1.07)
≤ 0.73 (n=304)	40	1.44 (1.30-1.60)	11	1.08 (1.03-1.13)

EPAC: Episodes of Poor Asthma Control. ASUI: Asthma Symptom Utility Index
**EPACs: Any one of the following: 1) peak flow decrease of ≥30% from personal best, 2) increased rescue medication use above the average reported during the two weeks before randomization, 3) new or increased oral corticosteroids for asthma, 4) an unscheduled use of healthcare for treatment of asthma*
*** Exacerbations: Any one of the following: 1) new or increased oral corticosteroids for asthma, 2) an unscheduled healthcare encounter for treatment of asthma*

Reliability of the ASUI

The internal consistency reliability (Cronbach's alpha) was 0.74 (n = 1223) in the SIIVA sample and 0.71 (n = 413) in the SARA sample indicating that all the individual items that comprise the ASUI do in fact measure the same construct. Test-retest reliability (intra class correlation coefficient) among the 13% (n=55) participants in the SARA trial who had stable asthma over a four week period was 0.76 indicating that the ASUI had good reproducibility over time.

Responsiveness of the ASUI

The ASUI demonstrated good responsiveness to change. As hypothesized, ASUI scores improved significantly among participants whose percent predicted FEV1 improved by greater than or equal to 10% compared to those with no change in percent predicted FEV1 (Table 6). Likewise, there was a significant change in ASUI scores (in the hypothesized direction) when ACQ scores changed by more than the minimally important difference of 0.5 points compared to when the ACQ scores were unchanged (Table 6). After adjusting for visit period, the GEE-based repeated measures analysis revealed that there was a statistically significant difference in mean change in ASUI scores between visits with an EPAC in the prior period and those without an EPAC ($P<0.0001$) [Table 7]. Similar significant differences were seen for all four EPAC components (Table 7).

Table 6: Mean changes in ASUI scores as a function of changes in percent predicted FEV1 values and ACQ scores (Baseline vs. end of follow-up) [SARA trial]

		N (pts.)**	Mean change in ASUI (95% CI)	P value
Changes in percent predicted FEV1				
Better (ΔFEV1 ≥ 10%)		213 (163)	0.05 (0.03, 0.07)	
Same (-10% ≤ ΔFEV1 <10%)		1657 (384)	0.01 (0.00, 0.01)	
Worse (ΔFEV1 ≤-10%)		222 (170)	-0.03 (-0.05, -0.02)	<0.0001
Changes in ACQ* (ΔACQ)				
Better	ΔACQ ≥ -0.5	442 (366)	0.15 (0.14, 0.17)	
Same	+0.5 > ΔACQ < -0.5	1254 (369)	0.00 (-0.00, 0.01)	
Worse	ΔACQ ≥ + 0.5	372 (297)	-0.15 (-0.16, -0.13)	<0.0001

Note: MID for ACQ is 0.5 points
ACQ: Asthma Control Questionnaire, ASUI: Asthma Symptom Utility Index, FEV1: Forced expiratory volume in the first second
**ACQ: Better = decrease by ≥ 0.5 points; same = change by <0.5 points; Worse = increase by ≥ 0.5 points.*
***N denotes frequency of events and "pts." indicates the number of patients*
GEE based repeated measures analysis with independent working correlation.

Table 7: Mean Difference is ASUI scores by EPAC status for all visits [SARA trial]

		ASUI		
	#EPAC (% visits)	**Mean difference***	**95% CI**	**P-value***
Any EPAC	750(35)	0.09	0.01, 0.10	<0.0001
EPAC components				
Peak flow drop	426(20)	0.08	0.06, 0.10	<0.0001
Rescue inhalers	414(19)	0.10	0.01, 0.12	<0.0001
Oral steroid use	168(8)	0.16	0.12, 0.20	<0.0001
Urgent care contact	103(6)	0.15	0.11, 0.20	<0.0001

2,155 follow-up visit periods evaluated among 390 participants
EPAC: Episodes of Poor Asthma Control.
ASUI: Asthma Symptom Utility Index
CI: Confidence Interval
**Mean difference in scores between visits with an EPAC in the prior period and those without an EPAC, adjusted for visit period;*
GEE based repeated measures analysis with independent correlation.

CHAPTER 4

DISCUSSION

We have presented a summary of some PRO instruments used in asthma clinical research. We then described the methodology for evaluating the psychometric properties of PRO instruments. Finally, we used the Asthma Symptom Utility Index (ASUI) as an example to demonstrate the procedures and methods used to evaluate the psychometric properties of an instrument.

Our results show that the ASUI, an asthma-specific utility index designed to summarize the frequency and severity of selected asthma-related symptoms[34] based on two week retrospective recall by the patients, has good psychometric properties in two groups of asthma patients. We confirmed the findings of Revicki et al.[34] that ASUI scores have an acceptable construct validity and discriminant validity[34]. We also showed that baseline ASUI scores have good predictive validity. Patients with the lowest baseline ASUI scores were 40% more likely to have an EPAC and 8% more likely to have an asthma exacerbation over the next two weeks compared to those with the highest baseline ASUI scores. The ability to predict EPACs and asthma exacerbations suggests that the ASUI could be useful in guiding asthma therapy in clinical practice. In addition, we have shown that the ASUI is responsive to changes in asthma control.

Some items on the ASUI are similar to those on other questionnaires that assess asthma control and asthma-related quality of life[11, 12, 16, 20, 23, 41, 51]. Asthma control as measured by the ACQ is a normative construct developed by physicians and validated against physician assessment of asthma[12, 41]. Asthma-related quality of life instruments measure the extent to which asthma symptoms interfere with physical functioning in daily life[16, 19, 20]. The ASUI focuses on the frequency and severity of asthma symptoms. In addition, it is a patient weighted, preference based scale and thus suitable for economic analyses that incorporate disability-adjusted life years[34].

A key strength of this analysis is that data from two separate trials conducted at different time periods, with different entry criteria, and different interventions were used. However, because of the differing study designs, we were not able to perform the same validation analyses in both trials. In both trials, we showed similar internal consistency reliability for the ASUI. This confirmed the findings of the original study by Revicki et al.[34] It was necessary to use data from both studies in order to fully characterize the psychometric properties of the ASUI. The SIIVA study included asthma patients with a wide range of clinical severity but ASUI was only administered at baseline[43], so test-retest reliability and longitudinal validity could not be assessed in this study population. Also patients in the SIIVA study had only 28 days of follow-up data, which may have limited the number of events, especially exacerbations. Nonetheless, because of the large population, we were able to demonstrate predictive validity based on the frequency of EPACS. In addition, ACQ scores and Mini AQLQ scores were not

available for the SIIVA study participants so construct validity could not be determined. The SARA trial which included multiple ASUI measurements provided a good opportunity to determine responsiveness[36].

Generalizability to other patient populations is an important aspect of health utility tools[40]. The initial development and validation of the ASUI included asthma patients who were relatively well educated and mostly White[34]. The current scoring of the ASUI in the United States is based on the multi-attribute utility function that was originally derived by Revicki et al. [34]. However, the preference weights, utility functions and mean ASUI scores derived in the United States[34] differ significantly from those obtained in other countries in Europe (Italy, France, and the United Kingdom)[52]. Nonetheless, the relative rank ordering of the mean ASUI scores in patients with asthma symptoms is maintained[52]. In the current analysis, we included participants with a good representation of women and racial minorities[36, 43]. Data on education level or socioeconomic status was not available. However, many of the study sites were located in large urban centers in the United States that generally serve patients of low socioeconomic status. Currently, the use of the ASUI has been largely limited to large epidemiological studies and clinical trials. The ASUI can be complex to calculate for an individual patient in the clinical setting compared to the ACT and this will limit its routine use in clinical practice. However, computers can address this problem.

The ASUI has been used as a secondary outcome measure is several asthma clinical trials[35, 36, 43]. It is typically used together with other asthma questionnaires

including the ACT, ACQ, MiniAQLQ etc. as well as asthma diaries. These have mostly been negative studies in terms secondary outcomes. Use of the ASUI to practically calculate disability-adjusted life years (DALYs) has not previously been performed.

In summary, we demonstrated that the ASUI has good psychometric properties among adult asthmatics when used in the context of clinical trials in the United States.

This work has been accepted for publication in the Journal of Allergy and Clinical Investigation (JACI).

APPENDIX

I. Copy of ASUI used in SIIVA and SARA trials

Asthma Symptom Utility Index *(Self-administered)*

1. **How, many days were you bothered by coughing in the past 2 weeks (check only one)**
   (1) Not at all → Skip to item 3, (2) 1-3 days, (3) 4-7 days, (4) 8-14 days
2. **On average, how severe was your cough during the past 2 weeks (check only one)**
   (1) Mild, (2) Moderate, (3) Severe
3. **How many days were you bothered by wheezing during the past 2 weeks (check only one)**
   (1) Not at all → Skip to item 5, (2) 1-3 days, (3) 4-7 days, (4) 8-14 days
4. **On average, how severe was your wheezing during the past 2 weeks (check only one)**
   (1) Mild, (2) Moderate, (3) Severe
5. **How many days were you bothered by shortness of breath during the past 2 weeks (check only one)**
   (1) Not at all → Skip to item 7, (2) 1-3 days, (3) 4-7 days, (4) 8-14 days
6. **On average, how severe was your shortness of breath during the past 2 weeks (check only one)**
   (1) Mild, (2) Moderate, (3) Severe
7. **How many days were you awakened at night by your asthma during the past two weeks (check only one)**
   (1) Not at all → Skip to item 9, (2) 1-3 days, (3) 4-7 days, (4) 8-14 days
8. **On average, how much of a problem was being awakened at night during the past 2 weeks (check only one)**
   (1) Mild, (2) Moderate, (3) Severe
9. **How many days were you bothered by side effects of asthma medications during the past 2 weeks (check only one)**
   (1) Not at all → Stop, (2) 1-3 days, (3) 4-7 days, (4) 8-14 days
10. **On average, how severe were the side effects during the past 2 weeks (check only one)**
    (1) Mild, (2) Moderate, (3) Severe

I. **Original method used to derive the Multi-symptom states that were included in the final equation for calculating the ASUI**

TABLE 8-- Mean VAS Preferences, SG Utilities, and ASUI-Derived Utilities for Multi-symptom States

State	VAS‡ Mean (SD)	SG Utility§ Mean (SD)	ASUI Mean
Corner states*			
Severe cough	0.26 (0.25)	0.69 (0.21)	0.70
Severe wheeze	0.24 (0.25)	0.66 (0.21)	0.67
Severe dyspnea	0.16 (0.21)	0.60 (0.25)	0.61
Severe awaken at night	0.25 (0.25)	0.67 (0.25)	0.68
Severe medication side effects	0.25 (0.26)	0.66 (0.23)	0.67
Multisymptom states†			
Moderate cough and dyspnea (1-3 d)	0.31 (0.25)	0.67 (0.23)	0.73
Moderate cough and wheeze (4-7 d)	0.22 (0.20)	0.62 (0.24)	0.56
Severe cough; moderate wheeze and dyspnea (1-3 d)	0.20 (0.20)	0.60 (0.21)	0.54
Severe cough; moderate wheeze, dyspnea, and awaken at night (1-3 d)	0.17 (0.18)	0.59 (0.24)	0.50
Severe cough, dyspnea, and awaken at night; moderate wheeze and side effects (1-3 d)	0.08 (0.12)	0.46 (0.27)	0.31

‡ The VAS (visual analog scale) and SG (standard gamble) utility scores are on a 0 to 1 scale with higher scores indicating better health.
§ ASUI-derived utility score based on multiattribute utility functions (see text for details).
* One symptom is described as severe for 8 to 14 days and remaining symptoms are not present.
†For multisymptom states if a symptom is not mentioned, it is described as mild in the health state.

Obtained from Revicki et al.[39]

II. Applying the Multiattribute Utility function to a theoretical asthma patient

TABLE 9 -- Multiattribute utility function on worst possible symptom state to no symptoms scale for ASUI*

Level, d	Symptom (Attribute)				
	Cough S_1	**Wheeze S_2**	**Dyspnea S_3**	**Awaken at Night S_4**	**Medication Side Effects S_5**
1 None	1.0	1.0	1.0	1.0	1.0
2 Mild, 1-3	0.985	0.962	0.946	0.955	0.970
3 Mild, 4-7	0.963	0.940	0.920	0.931	0.954
4 Mild, 8-14	0.935	0.913	0.885	0.899	0.930
5 Moderate, 1-3	0.955	0.913	0.892	0.909	0.924
6 Moderate, 4-7	0.920	0.886	0.860	0.880	0.900
7 Moderate, 8-14	0.875	0.851	0.818	0.845	0.862
8 Severe, 1-3	0.863	0.810	0.771	0.821	0.824
9 Severe, 4-7	0.813	0.772	0.729	0.781	0.789
10 Severe, 8-14	0.751	0.729	0.681	0.734	0.730

*Calculating ASUI scores is as follows: ASUI = 1.200 × (S_1 × S_2 × S_3 × S_4 × S_5) - 0.200. For example, if a person is classified as level 3 on cough (S_1), level 4 on wheeze (S_2), level 2 on dyspnea (S_3), level 3 on awaken at night (S_4), and level 2 on medication side effects (S_5), his or her ASUI score equals (1.200 [0.963 × 0.913 × 0.946 × 0.931 × 0.970] - 0.200) or 0.701.

Obtained from Revicki et al.[39]

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