

## Validation studies of asthma patient-reported outcomes: "We want more!"

Christine A. Sorkness, PharmD *Madison, Wis*

**Key words:** Validation, patient-reported outcomes, Asthma Control Questionnaire, composite score, asthma control

Asthma clinical research lacks adequate standardization and validation of outcomes, particularly those that are patient-reported measures. The Asthma Outcomes Workshop,<sup>1</sup> which was convened in 2010 by a consortium of several National Institutes of Health institutes and the Agency for Healthcare Research and Quality, began to address this deficiency, building on a prior statement from the American Thoracic Society and the European Respiratory Society.<sup>2</sup> National Institutes of Health leadership came from the National Heart, Lung, and Blood Institute and the National Institute of Allergy and Infectious Diseases. In the published overview Busse et al<sup>1</sup> state the workshop's 2 key objectives: (1) to establish standard definitions and data collection methodologies for validated outcome measures (core and supplemental) in asthma clinical research with the goal of enabling comparisons across trials and (2) to identify promising outcome measures for asthma clinical research and comment on their status and further validation needs. Three key chapters of the workshop provide recommendations for relevant asthma patient-reported outcomes (PROs): (1) composite scores of asthma control<sup>3</sup>; (2) quality of life<sup>4</sup>; and (3) symptoms.<sup>5</sup>

Guidance is also available from the US Food and Drug Administration, describing its approach to review and evaluate existing, modified, or newly created PRO instruments, specifically to support claims in approved medical product labeling.<sup>6</sup> Key considerations in the US Food and Drug Administration's evaluation of a PRO instrument include the population enrolled in the clinical trial, the clinical trial objectives and design, the instrument's conceptual framework, and the instrument's measurement properties. This US Food and Drug Administration guidance does not address disease-specific issues.

The Asthma Outcomes Workshop<sup>3</sup> designated 2 asthma control composite score instruments (Asthma Control Questionnaire [ACQ]<sup>7</sup> and the Asthma Control Test<sup>8,9</sup>) as core measures for National Institutes of Health-initiated clinical research in adults because of the importance of asthma control as a goal of therapy, extensive validation data for these instruments, and low patient burden and risk. At the time of the 2012 Workshop Report, the

ACQ had been used in the majority of published trials, and the Asthma Control Test had the most published validation data.

Cloutier et al<sup>3</sup> also assessed the Childhood Asthma Control Test<sup>10</sup> to have met the minimum standard as a core measure for participant characterization and observational studies because it had more validation data than other instruments for children ages 4 to 11 years. The Workshop Report considered the Childhood Asthma Control Test to be only supplemental for clinical trials until more responsiveness data and a minimal clinically important difference are published.

Cloutier's Workshop Report<sup>3</sup> section ended with a call for "We want more!" Specific identified needs included validation of the composite measures in population subgroups defined by age, race/ethnicity, socioeconomic status, health literacy, specific comorbidities, asthma severity or phenotype, or asthma treatment. Furthermore, the need to both confirm or define minimal clinically important differences for all instruments (to document change in a subject over time and differences in populations) and demonstrate responsiveness over time and to therapy was identified.

In this issue of the *Journal*, Nguyen et al<sup>11</sup> provide much-needed data on the reliability, validity, and responsiveness to change of the ACQ for assessing asthma control in children ages 6 to 17 years. A threshold value for poor disease control (an essential asthma phenotype) and a minimal clinically important difference were also determined. This report has several strengths that deserve emphasis. The data were collected during 8 study visits over 24 weeks from diverse children enrolled in a large (n = 305) 19-center clinical trial conducted by the American Lung Association's Asthma Clinical Research Centers called the Study of Acid Reflux in Children with Asthma.<sup>12</sup> The mean age of these children was 11 years (SD, 3 years); 50% of participants were black, and 11% were Hispanic. Multiple objective measures of asthma control, including asthma symptoms and physiology, were collected by using standardized procedures as validation for the PRO. The American Lung Association studies are widely recognized for their design quality and rigorous performance standards.

The authors concluded that the ACQ is moderately reliable and responsive to assess asthma control in 6- to 17-year-old children with poor asthma control, and they did not find meaningful differences between younger (6-11 year olds) and older (12-17 year olds) children for most of the selected outcomes.<sup>11</sup> Fair-to-good internal consistency, moderate test-retest reliability, and adequate validity and responsiveness were demonstrated. Importantly, changes in ACQ scores were different among patients with deteriorating, improving, or stable asthma symptoms. The optimal threshold for poor asthma control was 1.25 or greater, and the minimal clinically important difference was 0.40.

Nguyen et al<sup>11</sup> acknowledge some limitations in their validation study, as appropriate. Because of the small number of stable patients enrolled and the ineffectiveness of the reflux agent to

From the Departments of Pharmacy and Medicine, University of Wisconsin-Madison. Disclosure of potential conflict of interest: C. A. Sorkness declares that she has no relevant conflicts of interest.

Received for publication October 30, 2013; accepted for publication November 4, 2013.

Corresponding author: Christine A. Sorkness, PharmD, University of Wisconsin-Madison, 777 Highland Ave, Madison, WI 53705. E-mail: [sorkness@wisc.edu](mailto:sorkness@wisc.edu).

J Allergy Clin Immunol 2013;■■■:■■■-■■■.

0091-6749/\$36.00

© 2013 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2013.11.001>

improve asthma control in the patient study,<sup>12</sup> neither ACQ test-retest reliability nor responsiveness to beneficial treatment could be assessed. So be it. The authors clearly state that the North American English version of the 7-item ACQ was administered.<sup>7</sup> In children ages 6 to 10 years, the ACQ was completed with the assistance of an accompanying adult, either a parent or guardian, which is consistent with the findings of Guyatt et al.<sup>13</sup>

In conclusion, this issue's validation study provides needed and reassuring data to support the application of the ACQ to assess asthma control among children in clinical trials. Furthermore, as a member of the Study of Acid Reflux in Children with Asthma<sup>12</sup> Data and Safety Monitoring Board appointed by the National Heart, Lung, and Blood Institute, I know the authors used the ACQ in their trial with the permission and requirements of Dr Juniper and consistent with the instructions provided by Mapi at the time of trial conduct. Requirements for responsible investigative team conduct and use of authorized patient-reported outcome measure versions have been well articulated.<sup>14</sup> "We want more and more is better"<sup>15</sup> should continue to be the mantra of the asthma research community. Our ability to obtain accurate and reliable assessment of asthma control in clinical trials and compare across treatments requires the use of patient-reported outcome measures shown to be both responsive to change and stable when no clinically meaningful change has occurred. Such measures must be validated in broadly generalizable populations with asthma to be relevant and trusted.

## REFERENCES

1. Busse WW, Morgan WJ, Taggart V, Togias A. Asthma outcomes workshop: overview. *J Allergy Clin Immunol* 2012;129(Suppl):S1-8.
2. 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;180:59-99.
3. Cloutier MM, Schatz M, Castro M, Clark N, Kelly HW, Mangione-Smith R, et al. Asthma outcomes: composite scores of asthma control. *J Allergy Clin Immunol* 2012;129(Suppl):S24-33.
4. Wilson SR, Rand CS, Cabana MD, Foggs MB, Hatterman JS, Olson L, et al. Asthma outcomes: quality of life. *J Allergy Clin Immunol* 2012;129(Suppl):S88-123.
5. Krishnan JA, Lemanske RF Jr, Canino GJ, Elward KS, Kattan M, Matsui EC, et al. Asthma outcomes: symptoms. *J Allergy Clin Immunol* 2012;129(Suppl):S124-35.
6. Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims, December 2009. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071975.pdf>. Accessed October 1, 2013.
7. 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;14:902-7.
8. 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;113:59-65.
9. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, et al. Asthma Control Test: reliability, validity and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006;117:549-56.
10. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. *J Allergy Clin Immunol* 2007;119:817-25.
11. Nguyen JM, Holbrook JT, Wei CY, Gerald LB, Teague WG, Wise RA, et al. Validation and psychometric properties of the Asthma Control Questionnaire among children. *J Allergy Clin Immunol* 2013 [Epub ahead of print].
12. American Lung Association Asthma Clinical Research Centers, Holbrook JT, Wise RA, Gold BD, Blake K, Brown ED, et al. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. *JAMA* 2012;307:373-81.
13. Guyatt GH, Juniper EF, Griffith LE, Feeny DH, Ferrie PJ. Children and adult perceptions of childhood asthma. *Pediatrics* 1997;99:165-8.
14. Juniper EF. Medical questionnaires are copyrighted to ensure that validity is maintained. *Chest* 2009;136:951-2.
15. "We want more"/"more is better" [television commercial]. Dallas (TX): AT&T; 2013.