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Patient-Reported Outcome

Assessing Asthma Symptoms in Adolescents and Adults: Qualitative Research Supporting Development of the Asthma Daily Symptom Diary

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ABSTRACT

Background: Despite the widespread availability of patient-reported asthma questionnaires, instruments developed in accordance with present regulatory expectations are lacking. To address this gap, the Patient-Reported Outcome (PRO) Consortium's Asthma Working Group has developed a patient-reported asthma daily symptom diary (ADSD) for use in clinical research to assess outcomes and support medical product labeling claims in adults and adolescents with asthma. **Objectives:** To summarize the qualitative research conducted to inform the initial development of the ADSD and to provide evidence for content validity of the instrument in accordance with the Food and Drug Administration's PRO Guidance. **Methods:** Research informing the initial development and confirming the content validity of the ADSD is summarized. This comprised a review of published qualitative research, semi-structured concept elicitation interviews (n = 55), and cognitive interviews (n = 65) with a diverse and representative sample of adults and adolescents with a clinician-confirmed diagnosis of asthma in the United States to understand the asthma symptom experience and to assess the relevance and understanding of the newly developed ADSD. **Results:** From the qualitative literature review and concept elicitation interviews, eight core asthma symptoms emerged. These were broadly categorized as breathing symptoms (difficulty breathing, shortness of breath, and wheezing), chest symptoms (chest tightness, chest pain, and pressure/weight on chest), and cough symptoms (cough and the presence of mucus/phlegm). Conceptual saturation was achieved and differences in the experience of participants according to socio-demographic or clinical characteristics were not observed. Subsequent testing of the ADSD confirmed participant relevance and understanding. **Conclusions:** The ADSD is a new patient-reported asthma symptom diary developed in accordance with the Food and Drug Administration's PRO Guidance. Evidence to date supports the content validity of the instrument. Item performance, reliability, and construct validity will be assessed in future quantitative research.

Keywords: asthma, content validity, patient-reported outcomes, symptoms.

Introduction

Asthma is a chronic inflammatory disorder of the airways that causes recurrent episodes of coughing, wheezing, breathlessness, and chest tightness [1]. These episodes are usually associated with variable airflow obstruction that is often reversible, either spontaneously or with treatment [2]. The worldwide prevalence of asthma is estimated to be approximately 300 million, and it is expected to increase by 33% to 400 million by 2025 [3]. Despite advances in the understanding of asthma and broader availability of disease management guidelines, the proportion of patients with uncontrolled asthma remains high [4,5].

A number of objective methods for determining asthma disease severity exist. Forced expiratory volume in 1 second and peak expiratory flow, for example, typically serve as standard measurements of airway function in clinical studies. There is also

Conflicts of interest: At the time this research was conducted, J. Jason Lundy was associate director of the Critical Path Institute's Patient-Reported Outcome Consortium.

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increasing evidence to support the value of various biomarkers (including fractional exhaled nitric oxide, total Immunoglobin E, and blood eosinophils) [6]. Among the goals of asthma management (as highlighted in clinical guidelines), and an indicator of overall asthma control, is the eradication of or reduction in asthma symptoms [7–9]. Nevertheless, there is a poor correlation between the aforementioned objective measures of disease severity and patients' experience of asthma symptoms [10–12]. To provide a holistic understanding of patient disease severity and asthma control in clinical research, there is a need for standardized ways of assessing patients' experience of asthma symptoms.

Many symptoms of asthma can be known only to patients themselves and are therefore best reported via patient-reported outcome (PRO) instruments. Nevertheless, although there is no shortage of PRO instruments used in asthma studies, no instrument has been identified for the assessment of asthma symptoms that has been developed according to the regulatory expectations described by the US Food and Drug Administration (FDA) in its guidance for industry titled "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" (PRO Guidance) [13]. Indeed, a recent asthma outcomes workshop by the National Institutes of Health stated that "asthma clinical research will highly benefit from standardization of major outcomes in terms of definition and assessment methodology" [14] and concluded that no published asthma symptom diary had sufficient validation information to be chosen as a core asthma outcome for use in clinical research sponsored by the National Institutes of Health [15]. In particular, strong evidence supporting the content validity (the extent to which the PRO measures the concept of interest, i.e., asthma symptoms) of existing instruments in adolescents and adults with asthma is lacking.

To fill this gap, the PRO Consortium's Asthma Working Group (WG) at the Critical Path (C-Path) Institute [16] embarked on the development and qualification of the asthma daily symptom diary (ADSD) in collaboration with the FDA. The intent is for the ADSD to be used as a co-primary or secondary end-point in clinical trials to establish treatment outcomes and to support medical product labeling claims. This article summarizes the qualitative research conducted to inform the initial development of the ADSD and to provide evidence for content validity of the instrument in accordance with the FDA PRO Guidance.

Methods

Figure 1 summarizes the methods involved in the development of the ADSD. At each stage of this process, input was obtained from the Asthma WG, C-Path scientists, the expert panel (J.K., S.S., M.S., and J.H.), and representatives of the FDA Center for Drug Evaluation and Research via the formal Drug Development Tool qualification process [17].

Qualitative interviews during the development of the ADSD were conducted in accordance with the Declaration of Helsinki and approval was obtained from the Copernicus Group Independent Review Board (approval code ADE2-12-282).

Review of Existing Qualitative Literature

A targeted review of published qualitative research studies was conducted to identify the symptoms and effects experienced by adults and adolescents with asthma. Published peer-reviewed articles were identified via title and abstract searches in electronic bibliographic databases: MEDLINE, Embase, and PsycNFO. Disease (i.e., asthma), symptom and impact (i.e., symptom, control, health-related quality of life), and qualitative research (i.e., qualitative, phenomenology, thematic analysis, grounded theory, interview, focus group) medical subject headings (MeSH) terms or keywords were combined using Boolean logic commands. Searches were conducted in May 2012 and limited to articles published in English, concerning human subjects and published between 1997 and 2012.

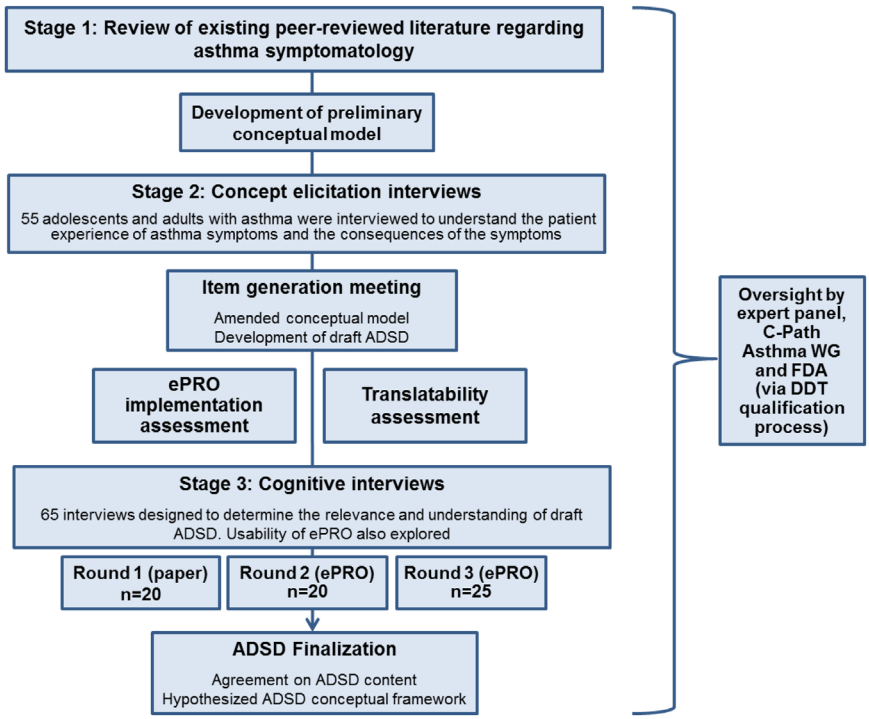

Fig. 1 – Overview of study methods. ADSD, asthma daily symptom diary; C-Path, Critical Path; DDT, drug development tool; ePRO, electronic patient-reported outcome; FDA, Food and Drug Administration; WG, Working Group. (Color version of figure available online).

All abstracts were reviewed by two independent researchers. For articles to be considered for full review, abstracts were required to reference asthma symptoms and/or impacts experienced by adults and/or adolescents. Abstracts were also required to reference qualitative research (e.g., patient interviews and focus groups) or analytic methods (e.g., grounded theory and thematic analysis). Articles were excluded if abstracts were not related to the experience of asthma symptoms/impacts as reported by the patient or an informant (e.g., parent). Abstracts referring only to asthma in infancy were also excluded.

Articles selected for full-text review were evaluated and salient information pertaining to study aim(s), sample demographic characteristics, methodology, and results were summarized. From the extracted information, key concepts relating to asthma symptoms and associated impact were identified and used to inform the development of a preliminary conceptual model outlining the experience of living with asthma as reported by patients.

Concept Elicitation Interviews

Concept elicitation interviews were conducted to provide a comprehensive understanding of the symptoms experienced by adults and adolescents with asthma and how they talk about these symptoms.

Recruitment

Forty-eight participants were targeted for inclusion in the interviews. This sample target was based on the projection that 12 interviews would be necessary to achieve conceptual saturation [18,19] in each of the four pre-specified age groups: 12 to 14 years, 15 to 17 years, 18 to 45 years, and 46 years and older. Note that (for adolescent participants in particular) exploration of the experience of asthma symptoms in narrow age bands was considered important to ensure the use of developmentally appropriate language in the resulting instrument [20].

Participants were recruited via referrals from primary care physicians/general practitioners or respiratory specialists from five geographically diverse sites in the United States (Los Angeles, New Orleans, Philadelphia/New Jersey, Pittsburgh, and St. Louis). To be eligible for inclusion, participants were required to meet the following inclusion/exclusion criteria:

1. a physician diagnosis of asthma, in accordance with national and international asthma guidelines (e.g., Expert Panel Report 3, Global Initiative for Asthma) [9,21] for at least 1 year;
2. to have filled a prescription for asthma medication in the year before recruitment and have experienced asthma symptoms during the 3 weeks before the interviews;
3. were non-smokers or had a cumulative history of less than 10-pack years;
4. were older than 12 years and provided written consent (and written parental assent received when relevant).

Participants were excluded from the study if they had

1. a diagnosis of a respiratory condition other than asthma (not including allergies or rhinitis);
2. any other significant lung, heart, gastrointestinal, or neurological disease;
3. any other physical, learning, emotional, or cognitive difficulties limiting ability to actively participate in an interview;
4. demonstrated a history of alcohol or drug abuse.

Recruitment quotas for the following characteristics were used to ensure a diverse and representative sample of participants: age, sex, ethnicity, race, education, level of asthma control, history of recent exacerbations, and medication use.

Interview procedure

All participants provided informed consent (or parental consent and participant assent in the case of participants aged 12–17 years) before their participation in the study. Semi-structured interviews (1 hour in duration) were conducted by trained qualitative researchers. Initial discussions were broad and open-ended to facilitate spontaneous elicitation of concepts. Probes were used to gather information on specific topics of interest (as informed by the qualitative literature review) only once every opportunity for spontaneous elicitation had been provided. Two creative exercises were also used to facilitate spontaneous elicitation of concepts during the interview, by having participants think about their condition from a different perspective. Specifically, participants were asked to discuss both a collage/picture (that they had created before the interview) and to select an animal representing their experience of asthma (see Appendix in Supplemental Materials found at http://dx.doi.org/doi:10.1016/j.jval.2016.01.007). All interviews were digitally recorded and transcribed verbatim.

Analysis

A qualitative analysis plan was developed a priori. A software package (ATLAS.ti [Scientific Software Development GmbH, Berlin, Germany]) was used to facilitate the storage, coding, and qualitative analysis of interview transcripts. To ensure that the concepts elicited by participants had been fully explored during the interviews, conceptual saturation was assessed. *Conceptual saturation* is defined as the point at which no new relevant or important information emerges with the collection of more data [13]. Participants were divided into three approximately equal groups on the basis of the chronological order in which interviews were conducted to allow the concepts elicited in each group to be compared using a stepwise approach. Saturation was judged to be achieved if no new concepts emerged in the final group of interviews. Analyses were conducted for the total sample and for subsamples according to age, sex, ethnicity, race, education, level of asthma control, history of recent exacerbations, and medication use.

Item Generation and Development of Draft Instrument

A 2-day item generation meeting was convened and attended by members of the Asthma WG (including sponsor, C-Path, and Adelphi Values representatives), the expert panel, and a linguistic validation specialist. Findings from the concept elicitation interviews were presented and discussed to reach consensus regarding key concepts for inclusion in an ADSD. During this meeting, draft items, instructions, response options, and a hypothesized conceptual framework were also developed. After the development of the draft instrument, an independent electronic implementation assessment (to determine the feasibility of migrating the instrument to electronic platforms) was conducted by representatives from seven electronic PRO (ePRO) system providers comprising the Instrument Migration Subcommittee of C-Path's ePRO Consortium. In addition, an in-depth translatability assessment involving representatives from six different cultures was conducted to determine the feasibility of translating/linguistically validating the instrument in other languages/cultures.

Cognitive Interviews

Semi-structured cognitive and usability testing interviews were conducted with adolescent and adult participants with asthma to evaluate the relevance and participant understanding of draft

ADSD items, instructions, response options, and ease of ADSD completion using the ePRO device.

Recruitment

A second (independent) sample of 65 participants was recruited in accordance with the aforementioned eligibility criteria used during the concept elicitation interviews. As previously mentioned, quotas were used to ensure that a diverse and representative sample of participants was recruited.

Interview procedure

Interviews were conducted in three separate successive rounds to allow for modifications to the ADSD and subsequent testing among participants. During the first round of interviews (n = 20), participants completed a paper version of the ADSD, whereas participants in rounds 2 (n = 20) and 3 (n = 25) completed an electronic version of the diary using a handheld ePRO device (HTC H2 smartphone [HTC Corporation, New Taipei City, Taiwan]). For all interviews, a semi-structured interview guide was used to guide the conducting of the interview and to ensure that all areas of the ADSD were discussed. Specifically, the first part of the interview involved a brief open-ended exploration of the participants' experience of asthma (i.e., concept elicitation). Subsequently, participants completed the morning or evening version of the ADSD (depending on the time of day of the interview: before midday or after midday) as part of a "think aloud" process in which participants were asked to speak their thoughts aloud as they read the instructions and completed the questions on the ADSD. After completion of this think aloud exercise, participants took part in both top-level and in-depth cognitive interviews centered on their experience of completing the ADSD and the relevance and understanding of the diary items, instructions, and response options. Usability of the ePRO device (i.e., whether respondents could use the electronic device and software appropriately) was also explored in rounds 2 and 3. All interviews were audio-recorded and transcribed verbatim for the purposes of qualitative analysis.

Analysis

Qualitative analysis of interview transcripts was conducted in accordance with the qualitative analysis plan and focused specifically on whether the content of the newly developed draft symptom diary was relevant, appropriate, understood, and interpreted consistently by participants.

Results

Review of Existing Peer-Reviewed Literature

Searches returned a combined total of 244 abstracts. Only 45 abstracts met the pre-specified criteria for inclusion; nevertheless, after full-text review, 27 more articles were omitted because they did not contain content relevant to this review as was expected from their abstracts. Therefore, a final total of 18 articles were included in the review [22–39].

The 18 identified articles reported qualitative research studies conducted worldwide with an ethnically and racially diverse sample of adults and/or adolescents with asthma (Table 1).

Only two articles reported findings from adolescents aged 11 to 18 years [25,39]; six of the articles, however, reported results from mixed samples of children and adolescents aged between 6 and 18 years [23,27,28,30,35,37]. Comparable qualitative methodologies were used, including semi-structured interviews [23,28,30–34,36,37], focus groups [22,24–27,35], or a combination of both [29,38].

Core asthma symptoms reported in the literature fell into three categories: breathing symptoms (e.g., difficulty breathing, shortness of breath, and wheezing), chest symptoms (e.g., chest tightness, chest pressure, and chest pain), and cough symptoms (sometimes including the presence of mucus/phlegm). A range of additional (co-occurring but not disease-defining) symptoms were identified. Symptoms were identified as occurring during the day or at night, with the impact of such symptoms mediated by factors such as symptom frequency, duration, and severity/intensity. In addition, asthma was reported to have impacts on patients' physical functioning, emotional/psychological well-being, sleep, social life/relationships, education, and work. Based on these findings, a preliminary conceptual model of the patients' experience of asthma was developed, which was subsequently validated using findings from concept elicitation interviews described herein (Fig. 2).

Concept Elicitation Interviews

Participants' socio-demographic and clinical characteristics

A total of 55 adolescents (n = 25) and adults (n = 30) with asthma were recruited for participation. Pre-specified recruitment quotas were met, as reflected in the diverse socio-demographic and clinical characteristics of the sample (Table 2).

Identification of symptom concepts

During the course of the interviews, a total of 70 distinct symptoms were spontaneously elicited by participants. Of these 70 symptoms, 8 symptoms emerged as the "core" symptoms of asthma on the basis of the frequency at which they were spontaneously reported by study participants (Table 3). Consistent with the findings of the qualitative literature review, these core symptoms included *breathing symptoms* (i.e., difficulty breathing, shortness of breath, and wheezing), *chest symptoms* (i.e., chest tightness, pressure/weight on chest, and chest pain), and *cough symptoms* (i.e., cough and presence of mucus and phlegm). Of the 62 "non-core" symptoms, the most frequently mentioned were those that were more commonly associated with allergies (e.g., sneezing [n = 14] and stuffy nose/nasal congestion [n = 9]), were non-specific (e.g., tiredness [n = 14] and headache [n = 7]), or were known adverse effects of existing asthma medications (e.g., throat discomfort [n = 15] and sore throat [n = 9]). Consensus among the expert panel, supported by the literature review findings, confirmed that none of these symptoms should be considered as core symptoms of asthma.

Subgroup analyses according to age quotas, sex, asthma control, recent exacerbation, and the Expert Panel Report 3 medication steps confirmed the elicitation of the eight core symptoms of asthma across all subgroups, with no symptom found to be specific to or not to occur in a single subgroup. Although variations in the timing, severity, and duration of symptoms were observed, conceptual definitions were remarkably consistent. In particular, terms used by adults and adolescents to refer to their symptoms were similar.

In the total study sample, 63 of 70 (90.0%) individual symptoms were elicited within the first two sets of interviews (n = 37 of 55 participants). Only seven symptoms were mentioned by participants for the first time in the final set of interviews (these, however, were judged to be primarily related to allergic rhinitis and hay fever): itchy eyes (n = 3), allergies (n = 2), itchy nose (n = 2), loss of voice (n = 2), nasal congestion/stuffy nose (n = 2), watery eyes (n = 1), and swelling of eyes (n = 1). Therefore, findings suggest that conceptual saturation was achieved. Furthermore, conceptual saturation was demonstrated for the eight core symptoms across all the 21 groups defined according to sub-quotas for age, sex, ethnicity, race, education, asthma control, history of recent exacerbations, and steps of medication.

Table 1 – Qualitative literature review—overview of study samples and socio-demographic characteristics.

Reference	Sample size	Study country	Participant group	Age (y)	Sex	Race/ethnicity/nationality	Interviews/ focus groups
Ayala et al. [25]	n = 50	USA	Adolescents	12–17 (n = 50)	Male (n = 22) Female (n = 28)	White (n = 24); African American (n = 20); others (not specified) (n = 6)	Focus groups
Baptist et al. [22]	n = 46	USA	Adults	>18 (n = 46)	Not specified	White (n = 23); African American (n = 20); others (not specified) (n = 3)	Focus groups
Callery et al. [28]	n = 25	UK	Children and their parents Adolescents and their parents	9–11 (n = 12) 12–16 (n = 13)	Male (n = 16) Female (n = 9)	Not specified	Interviews
Chiang [37]	n = 11	China	Children and their parents Adolescents and their parents	6–12 (n = 11)	Male (n = 6) Female (n = 5)	Not specified	Interviews
Edgecombe et al. [39]	n = 22	UK	Children Adolescents	11–18	Male (n = 16) Female (n = 6)	Not specified	Interviews
Gabe et al. [30]	n = 55	UK	Children Adolescents	11–16	Male (n = 28) Female (n = 27)	White*	Interviews
Hussein and Partridge [29]	n = 60	UK	Adolescents Adults	16–50	Not specified	Pakistani* Indian*	Interviews Focus groups
Ostergaard [33]	n = 20	Denmark	Parents of children and adolescents	2–15	Not specified	Not specified	Interviews
Pradel et al. [23]	n = 32	USA	Children Adolescents	7 (n = 19) 12 (n = 13)	Male (n = 20) Female (n = 12)	White (n = 16) African American (n = 15) Native American (n = 1)	Interviews
Protudjer et al. [32]	n = 22	Canada	Children	11	Male (n = 11) Female (n = 11)	Not specified	Interviews
Rudell et al. [38]	n = 55	UK, France, Germany, USA	Adolescents Adults	18–90	Male (n = 20) Female (n = 35)	Not specified	Focus groups
Trollvik et al. [34]	n = 15	Norway	Children	7–10	Male (n = 9) Female (n = 6)	Not specified	Interviews
Tumiel-Berhalter and Zayas [24]	n = 22	USA	Adults (reporting about their asthma or proxy reports about their child's asthma)	>18	Not specified	Not specified	Focus groups
Turner-Bowker et al.[26]	n = 21	USA	Adults	25–59	Male (n = 8) Female (n = 13)	White (n = 16) African American (n = 4) Asian (n = 1)	Focus groups
Van Dellen et al. [35]	n = 40 (children and 28 of their mothers)	Netherlands	Children Adolescents	7–17	Male (n = 27) Female (n = 13)	Dutch* Moroccan* Turkish* Surinamese*	Focus groups
van den Bemt et al. [36]	n = 25	Netherlands	Children	6–11	Male (n = 16) Female (n = 9)	Not specified	Focus groups
Vincent et al. [31]	n = 25	Australia	Adults	22–75	Male (n = 11) Female (n = 14)	Not specified	Interviews
Walsh et al. [27]	n = 40	USA	Children Adolescents	8–17	Not specified	White (non-Hispanic)* African American* Hispanic*	Focus groups

* Sample proportion not specified.

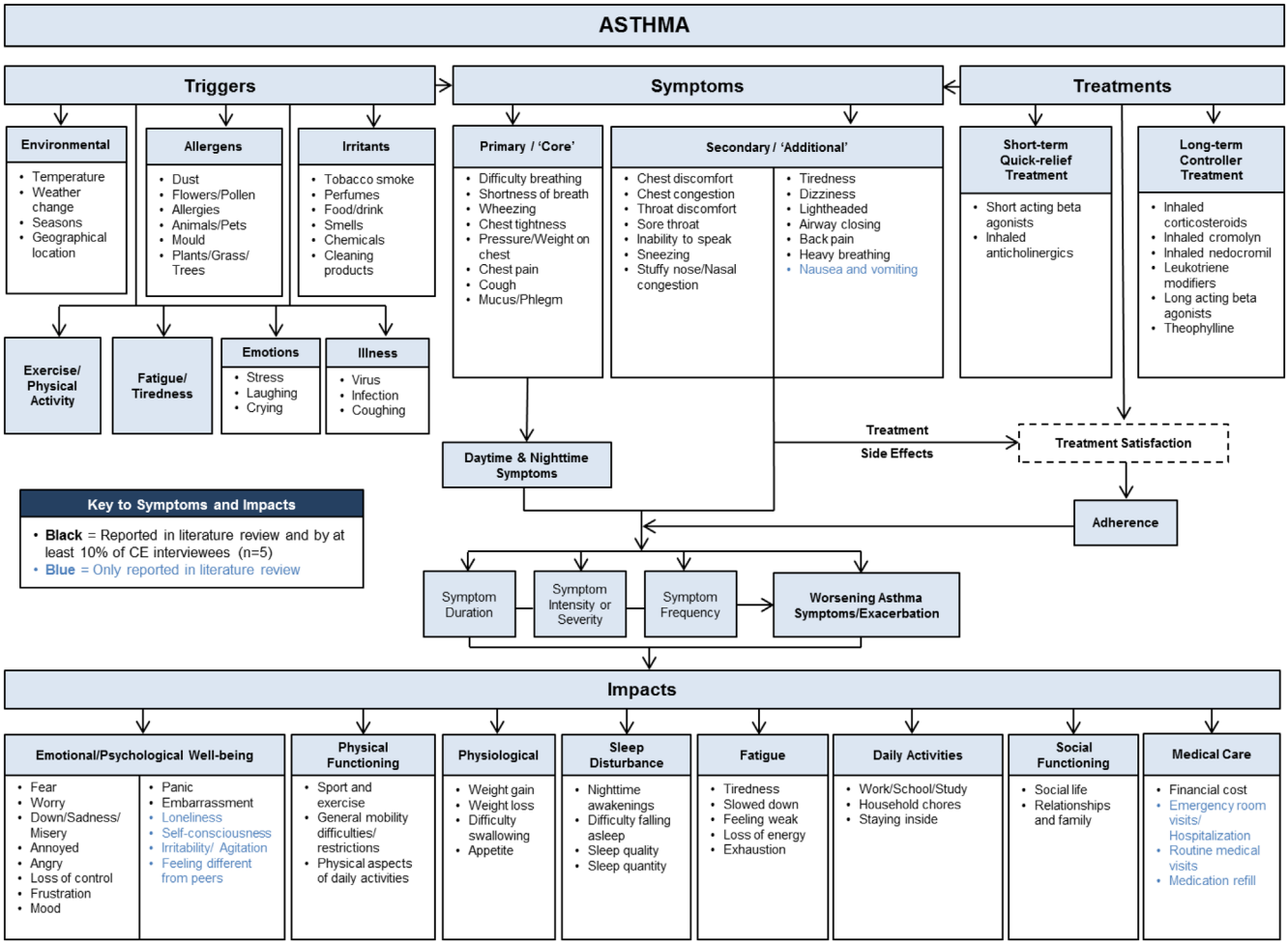

Fig. 2 – Conceptual model of asthma symptom experience in adults and adolescents. (Color version of figure available online).

Item Generation

Given the aforementioned consistency in findings across participants, it was decided to operationalize the assessment of the eight core symptoms of asthma via a single diary suitable for use in adults and adolescents aged 12 years or older. A daily diary format was chosen to minimize the impact of recall bias and to account for the day-to-day variation in asthma symptoms. This format also facilitated both the calculation of symptom-free days and the assessment of changes in symptom severity over time.

Informed by findings from the literature review, concept elicitation interviews, input from the expert panel, and findings of the ePRO implementation assessment and translatability assessment, it was decided that

1. patient experience of symptoms should be evaluated in terms of severity (not frequency or bothersomeness). In particular, use of a daily diary format was considered to negate the need to assess symptom frequency and there is evidence of a lack of conceptual equivalence of "bother" or "bothersomeness" across cultures and languages [40].
2. respondents should be asked to rate each individual symptom at its "worst" because this is consistent with the FDA PRO Guidance [13] and most representative of the burden experienced by respondents [41].
3. each symptom would be rated using a 0 to 10 numeric rating scale (NRS) ranging from "not at all" to "as bad as you can imagine." Numeric ratings on a 0 to 10 scale were used spontaneously by participants during the concept elicitation interviews and have the advantage of offering greater gradation of response options (promoting responsiveness/sensitivity to change). It was also noted that NRS scales can be universally applied cross-culturally and across languages.
4. the diary should be completed twice daily because of the variability in symptom occurrence (daytime vs. nighttime) reported by participants. Twice-daily completion would promote accuracy in reporting and also minimize any potential recall bias: in the morning (on waking) to best capture respondents' experience of symptoms at night when typically asleep and in the evening (before going to bed) to best capture the experience of symptoms throughout the daytime when people typically carry out their usual activities.
5. bolding, underlining, capitalization, or use of italics to place emphasis on certain terms should be avoided because of problems in applying similar formatting consistently across all electronic platforms and in all alternate languages.

A single item was generated for seven of the eight core symptoms. Two items were generated for mucus/phlegm (i.e., feeling of mucus/phlegm in the chest and coughing up mucus/phlegm). Furthermore, although not part of the "core" ADSD, four additional items assessing important attributes of asthma control were developed: nighttime awakenings, number of "times" the

Table 2 – Participants' socio-demographic and clinical characteristics for concept elicitation and cognitive interviews.

Sample demographic and clinical data	Concept elicitation interviews					Cognitive interviews				
	12–14 y (n = 12)	15–17 y (n = 13)	18–45 y (n = 16)	≥46 y (n = 14)	Total (n = 55)	12–14 y (n = 18)	15–17 y (n = 17)	18–45 y (n = 15)	≥46 y (n = 15)	Total (n = 65)
Age, n (y)										
Mean	13	16	34	57	31	13	16	32	57	28
Min., Max.	12, 14	15, 17	18, 45	46, 76	12, 76	12, 14	15, 17	19, 45	46, 69	12, 69
Sex, n (%)										
Male	9 (75)	6 (46)	4 (25)	6 (43)	25 (45)	11 (61)	8 (47)	6 (40)	4 (27)	29 (45)
Female	3 (25)	7 (54)	12 (75)	8 (57)	30 (55)	7 (39)	9 (53)	9 (60)	11 (73)	36 (55)
Ethnicity, n (%)										
Hispanic or Latino (of any race)	2 (17)	2 (15)	5 (31)	1 (7)	10 (18)	6 (33)	5 (29)	5 (33)	3 (20)	19 (29)
Non-Hispanic or Latino	10 (83)	11 (85)	11 (69)	13 (93)	45 (82)	12 (67)	12 (71)	10 (67)	12 (80)	46 (71)
Race, n (%)										
White	4 (33)	7 (54)	5 (31)	9 (64)	25 (45)	5 (28)	6 (35)	8 (53)	6 (40)	25 (38)
Black/African American	4 (33)	3 (23)	6 (38)	4 (29)	17 (31)	3 (17)	1 (6)	4 (27)	5 (33)	13 (20)
Multi-racial	1 (8)	0	4 (25)	0	5 (9)	4 (22)	5 (29)	2 (13)	1 (7)	12 (18)
Others	3 (25)	3 (23)	1 (6)	1 (7)	8 (15)	6 (33)	5 (29)	1 (7)	3 (20)	15 (23)
Education level (adults aged ≥18 y only), n (%)	NA	NA			N = 30	NA	NA			N = 30
Some high school			5 (31)	4 (29)	9 (30)			3 (20)	7 (47)	10 (33)
College or higher			11 (69)	10 (71)	21 (70)			12 (80)	8 (53)	20 (67)
Asthma control according to patient score on asthma control test, n (%) [43]										
Well-controlled (≥20)	5 (42)	3 (23)	2 (13)	6 (43)	16 (29)	7 (39)	5 (29)	5 (33)	3 (20)	20 (31)
Not well-controlled (16–19)	4 (33)	6 (46)	6 (38)	2 (14)	18 (33)	6 (33)	6 (35)	5 (33)	1 (7)	18 (28)
Very poorly controlled (≤15)	3 (25)	4 (31)	8 (50)	6 (43)	21 (38)	5 (28)	6 (35)	5 (33)	11 (73)	27 (42)
Experience of an exacerbation in the 3 wk before screening according to physician, n (%) [44]										
No exacerbation	2 (17)	5 (38)	3 (19)	8 (57)	18 (33)	8 (44)	7 (41)	7 (47)	7 (47)	29 (45)
Moderate exacerbation	6 (50)	8 (62)	10 (63)	4 (29)	28 (51)	6 (33)	4 (24)	7 (47)	6 (40)	23 (35)
Severe exacerbation	4 (33)	0	3 (19)	2 (14)	9 (16)	4 (22)	6 (35)	1 (7)	2 (13)	13 (20)
Medication step, n (%) [9]										
Step 1	2 (17)	1 (8)	2 (13)	0	5 (9)	3 (17)	3 (12)	4 (27)	2 (13)	12 (18)
Step 2	2 (17)	3 (23)	0	2 (14)	7 (13)	3 (17)	2 (6)	3 (20)	0	8 (12)
Step 3	6 (50)	4 (31)	3 (19)	3 (21)	16 (29)	7 (39)	10 (59)	5 (33)	4 (27)	26 (40)
Steps 4–5	2 (17)	5 (38)	8 (50)	9 (64)	24 (44)	5 (28)	2 (12)	1 (7)	7 (47)	15 (23)
Step 6	0	0	3 (19)	0	3 (5)	0	0	2 (13)	2 (13)	4 (6)

Max., maximum; Min., minimum; NA, not available.

Table 3 – Summary of core symptoms to emerge from concept elicitation interviews.

Symptom	Frequency of participants reporting symptom: spontaneous (S) and probed (P)	Supporting quote (participant ID*)
	Breathing symptoms	
Difficulty breathing	S-55 Total n = 55 (100%)	Q: "And tell me what it's like to have asthma." "Well … it interferes, um, with my breathing." Q: "How does it interfere with your breathing?" "Um, I – I have wheezing. I have difficulty breathing." (101-F-65-WC)
Wheezing	S-39; P-7 Total n = 46 (83.6%)	Q: "OK. OK. When – when do you decide to use the machine? When is – what – what has to be going on to make you decide, oh, better – better – use the machine?" "When I wake up – I say, ooh, I feel I'm shortness of breath. You know? Or my husband can hear me wheeze or – like there's a wheezle. And he'll just plug it up – then." (311-F-45-VPC)
Shortness of breath	S-37; P-2 Total n = 39 (70.9%)	Q: "And then, what would the symptoms be of asthma that you would experience?" "Um, well, it's just the wheezing, the shortness of breath, um, and then, I get – my nose, but no, other than that." (107-F-17-NWC)
	Chest symptoms	
Chest tightness	S-36; P-4 Total n = 40 (72.7%)	Q: "What would a typical day of asthma symptoms be like for you?" "Well, that congestion – that head fog, the feeling like tightness in my chest like I can't breathe …." (102-F-44-NWC)
Chest pain	S-29; P-7 Total n = 36 (65.6%)	Q: "What else happens on a bad day with asthma? What kind of symptoms might you have on a bad day?" "I'll just have like tightness in my chest. And it'll – you know, if it goes on long enough, which is why I carry my inhaler with me, if it goes on long enough then probably at the end of the day or something – it's like when I'm forcing myself to breathe it causes chest pains." (304-F-19-VPC)
Pressure/weight on chest	S-25 Total n = 25 (45.5%)	Q: "I see you're making a fist." "Right. Uh, it – because it – it – I – I can feel it as the heavi – heaviness starts, um, and – and it's just a heaviness in, uh, my, I – I guess the – right at – right at the top of my chest." (306-F-54-NWC)
	Cough symptoms	
Cough	S-42; P-7 Total n = 49 (89.1%)	Q: "So what is the cough like?" "Sometimes it's a dry cough. And sometimes it's a real mucousy cough, but it starts out – it'll start out dry." (501-F-55-VPC)
Mucus/phlegm	S-22; P-13 Total n = 35 (63.6%)	Q: "Tell me more about that." "Well, when I – when I, um – it – like, it's – it plays a part, like, when I'm – if I'm wheezing, I'm going to cough and I'll be trying to cough, you know, like, mucus out or something, trying to clear it quick." (307-M-44-NWC)

* Participant IDs are presented as follows: participant ID number-sex (M = male; F = female)-age (y)-level of asthma control (WC = well-controlled, NWC = not well-controlled, VPC = very poorly controlled).

relief inhaler was used, number of "puffs" on the relief inhaler, and impact of symptoms on usual activities.

Cognitive Interviews

Participants' socio-demographic and clinical characteristics

A combined total of 65 participants with asthma participated in three rounds of cognitive interviews. All predefined quotas established at the outset of the study were again met, ensuring representation and diversity in the recruited sample (see Table 2).

Conceptual coverage

Participant-directed, open-ended discussion at the beginning of the cognitive interviews corroborated the results from the concept elicitation interviews and confirmed that the items of the ADSD encompassed all the symptoms considered by participants as important for understanding their asthma experience. The relevance of ADSD symptom concepts for participants (from highest to lowest) was as follows: difficulty breathing (n = 63 [96.9%]), cough (n = 63 [96.9%]), shortness of breath (n = 62 [95.4%]), wheezing (n = 61 [93.8.%]), chest tightness (n = 61 [93.8%]), chest pressure (n = 59 [90.8%]), mucus/phlegm in the chest (n = 57 [87.7%]), and chest pain (n = 43 [66.1%]). Thirty-five participants (53.8%) reported being woken up from their sleep because of their asthma symptoms. Almost all participants (n = 50 of 54 [92.6%]) reported limitations in their usual activities when asked specifically about the impact of their asthma symptoms. Similarly, almost all participants (n = 63 [96.9%]) reported using a quick relief inhaler in response to experiencing asthma symptoms.

ADSD understanding and comprehension

Overall, ADSD items and instructions were generally well understood and consistently interpreted across all age groups and education levels (Table 4). As a result, very few changes were implemented throughout the three rounds of interviews, with most of the items and instructions retaining their wording

Table 4 – Summary of feedback during cognitive interviews.

ADSD content	Supporting quote (participant ID*)
	ADSD items
Item 1. Difficulty breathing	"Um, to me, it means like you have problems breathing, that like you're not g – getting like enough air, and you're like about to like pass out." (411-F-12-VPC)
Item 2. Wheezing†	"It's kind of a like raspy, it's hard to describe … it kind of sounds like an insect's buzz. It kind of sounds like that, and it's really difficult to inhale." (302-M-15-WC)
Item 3. Shortness of breath	"Just like you can't catch your breath. Like it feels like you just like ran a mile." (410-M-19-NWC)
Item 4. Pressure/weight on chest	"Feels like somebody's – something is sitting on my chest with a lot of weight." (106-F-60-WC)
Item 5. Chest tightness	"Um, tightness as far as like your lungs not being able to expand." (209-M-48-VPC)
Item 6. Chest pain	"I guess a sharpness – a sharp sensation in, uh – in your lungs." (102-M-49-NWC)
Item 7. Cough	"I do cough a lot – and it does affect me. And it can sometimes like bother me right here because I'm coughing so much (pointing to throat)." (111-M-13-NWC)
Item 8. Mucus/phlegm	"Uh, that means to me that there's substances in my lungs, like mucus and stuff." (108-M-15-NWC)
Item A (M). Nighttime awakenings	"Out of all my asthma symptoms, in the middle of the night did I ever wake up because of one of them?" (109-M-13-NWC)
Item A (E). Impact on daily activities	"It's asking me how – how much has my asthma interfered with me getting things done." (110-F-33-NWC)
Item B1. Times used quick relief inhaler	"It's like how many times did – did I need to take my inhaler?" (207-F-24-NWC)
Item B2. Puffs of quick relief inhaler	"It's how many times I pressed down on the inhaler." (108-M-15-NWC) "Puffs is every time you inhale and exhale." (306-F-50-VPC)
	General features of the ADSD
Recall period	"I rated how I felt before I went to bed last night. So around before I went to bed I – and took a snapshot in time in my brain, OK, how did I feel at that time?" (401-F-39-WC) "I was thinking about just the time I'd gotten out of bed to now." (104-F-14-WC)
Response continuum	"Oh, it's a pretty good scale, I guess, um. Makes sense. Uh, I could rate it from zero to 10 pretty easily." (318-M-15-NWC)
ePRO usability (rounds 2 and 3 only)	"It was very, very easy. It felt like the operating system worked really well." (414-M-29-VPC) "It made it easy for me, because I use a smartphone. So I use applications like this all the time, and they're pretty much the similar size." (110-F-33-NWC)

ADSD, asthma daily symptom diary; ePRO, electronic patient-reported outcome.

* Participant IDs are presented as follows: participant ID number-sex (M = male; F = female)-age (y)-level of asthma control (WC = well-controlled, NWC = not well-controlled, VPC = very poorly controlled).

† Wheezing as assessed on the ADSD is inclusive of both the sensation and the associated sound of wheezing. Wheezing is measured using a single item and does not represent an item assessing multiple concepts (e.g., double enquiry).

throughout. When changes were implemented on the basis of participant feedback, these were only minor.

On the basis of the results from the three rounds of interviews, it was agreed that no further symptoms needed to be added to the draft ADSD. Nevertheless, on the basis of the results of the first two rounds of interviews, the Asthma WG agreed that the item assessing coughing up mucus/phlegm should be removed before the testing in round 3. This was primarily because of conceptual overlap and redundancy with items assessing cough and the feeling of mucus/phlegm in the chest that had led to some confusion among a small number of participants. Findings from round 3 confirmed that the remaining items were well understood and interpreted consistently by participants.

When asked about completing the diary twice a day, most participants (n = 57 [87.7%]) stated that it was important to assess their asthma symptoms twice a day because of the variability in their experience of symptoms during the day and at nighttime. When understanding of the specified recall periods was explored, almost all participants (n = 61 [93.8%]) provided feedback consistent with understanding of the recall period instructions.

Response options for ADSD appeared to be well understood and consistently interpreted by participants. Most participants who were asked (n = 57 of 63 [90.4%]) found the NRS easy to complete and preferable to having verbal response options. Consideration of participant responses to the morning and evening diary during the interviews revealed endorsement of options for individual items across the entire response continuum (from 0 to 10).

Participant feedback supported the ease of completing the ADSD on the ePRO device, and no issues with presentation, selection of responses, or navigating through the instrument were identified. Furthermore, no differences in participant understanding and the response options selected by participants were observed depending on whether the ADSD was completed in portrait or landscape orientation.

After the completion of the three rounds of cognitive interviews, a meeting was convened between the Asthma WG and the expert panel. Findings from the cognitive interviews were discussed and there was agreement to retain the items assessing the eight core symptoms of asthma (as tested in round 3 of the cognitive interviews) for testing in the planned quantitative pilot study. On the basis of the feedback from the expert panel, an optional item that could be used to assess nebulizer use in clinical trials (as per sponsor requirements) was developed. This item was developed using language parallel to items assessing relief inhaler use and tested in the cognitive interviews. The hypothesized ADSD conceptual framework is presented in Figure 3 and will be finalized after the completion of a planned quantitative study to explore content validity.

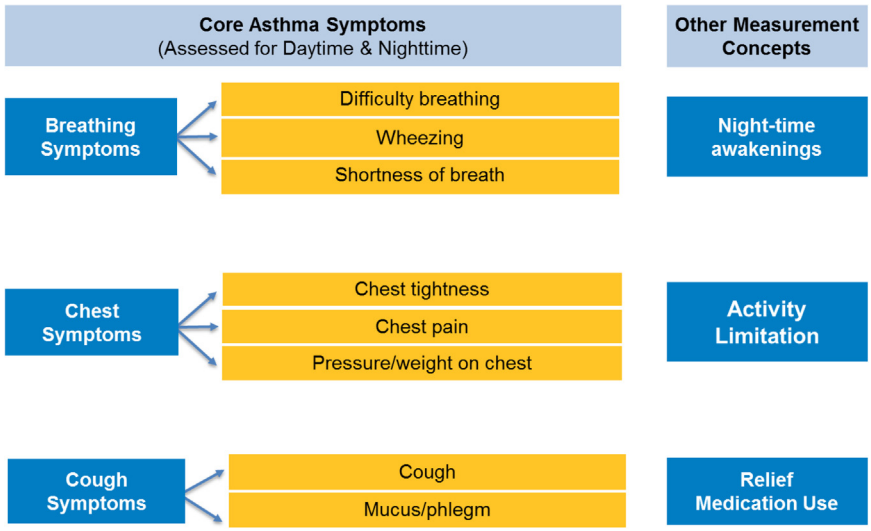

Fig. 3 – Hypothesized ADSD conceptual framework (this is to be finalized after the completion of the quantitative study to explore content validity). ADSD, asthma daily symptom diary. (Color version of figure available online).

Discussion

The ADSD has been developed by a multidisciplinary team (involving representatives from 13 pharmaceutical firms, the C-Path PRO Consortium, PRO consultants, and expert panelists) in close accordance with the best available standards for PRO development outlined in the FDA PRO Guidance [13]. Importantly, extensive involvement of a demographically and clinically diverse sample of adults and adolescents with asthma via qualitative research (in the generation and evaluation of content of the ADSD) has been comprehensively documented.

Research supporting the development of the ADSD highlights a consistency in the way in which adults and adolescents with asthma talk about their symptoms (regardless of demographic or clinical differences). This is reflected in the eight core symptoms of asthma that are assessed as part of the ADSD. The ADSD seeks to ameliorate issues with existing instruments assessing asthma symptom severity in terms of inadequate or incomplete conceptual coverage (no existing PRO instruments assess all eight symptoms), use of recall periods that require participants to average over time or think back to an earlier state, inclusion of single items measuring multiple concepts, and use of response options that may limit ability to distinguish between asthma states and to demonstrate change in symptoms over time [42]. The authors acknowledge the publication of a recent asthma symptom diary by Globe et al. [43] after the completion but before the publication of this research, which goes some way in addressing some of the aforementioned limitations of existing instruments [43]. Nonetheless, there are key differences between the ADSD and this aforementioned instrument: the ADSD assesses eight rather than four asthma symptoms and assesses asthma severity using a 0 to 10 NRS as opposed to a five-point verbal rating scale. It should also be noted that content generation and validation of the ADSD has paid careful attention in ensuring relevance and comprehension among diverse groups of patients varying according to socio-demographic (e.g., age, sex, race, ethnicity, and education level) and clinical (e.g., asthma severity and medication) characteristics, which have to date been largely ignored.

Content validity is typically established by evidence from qualitative studies that the content of the PRO instrument (items, instructions, response options, etc.) adequately reflects the intended measurement concepts. The PRO instrument should reflect the way in which the target population understand and discuss these concepts [13,44]. It is important to establish content validity before other measurement properties are evaluated because evidence of other types of validity (e.g., construct validity) or reliability (e.g., reproducibility of scores) will not overcome problems with content validity [13]. As the next step in the development of the ADSD, a pilot quantitative study is planned to generate further evidence to support the content validity of the instrument and to provide initial insights into item performance, reliability, and construct validity. Future plans include examining the ADSD's psychometric properties, including its ability to detect meaningful change in asthma symptom severity, using data collected in longitudinal treatment trials.

Conclusions

The ADSD was developed to facilitate comprehensive and reliable assessment of asthma symptoms from a patient's perspective. Evidence from extensive qualitative research provides support for the content validity of the instrument in adults and adolescents. Future research will seek to generate quantitative data to provide further evidence of content validity and insights into the reliability and psychometric validity of the ADSD.

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Supplementary Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2016.01.007 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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