

# Development of the Initial Version of the Asthma Daily Symptom Diary

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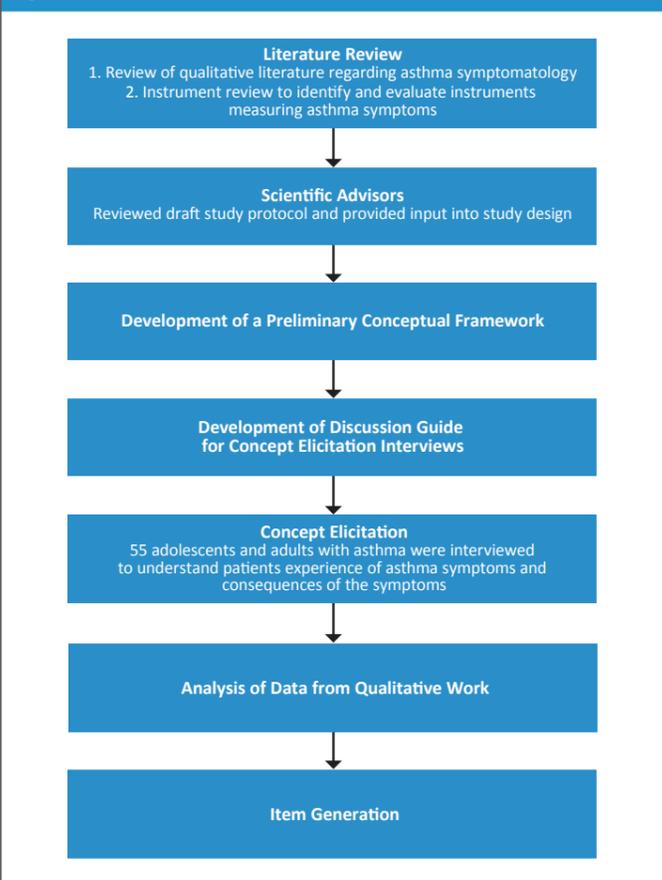
## Background

- The Asthma WG aims to develop a self-reported symptom diary for adults and adolescents with a diagnosis of mild to severe persistent asthma
- The FDA's Patient-Reported Outcome (PRO) Guidance recommends that PRO instrument development is based directly on patient input
- A review of prior qualitative research showed asthma was characterized by three core symptom domains: breathing symptoms (e.g., difficulty breathing, shortness of breath, wheezing), chest symptoms (e.g., tightness, pressure, pain), and cough-related symptoms (e.g., cough)
- A review of existing asthma symptom measures demonstrated that there currently is no instrument for the measurement of patient experience of asthma symptoms which meet standards specified in the FDA PRO Guidance for labeling claims (Nelsen et al, 2014)<sup>2</sup>
- This poster describes the concept elicitation interviews conducted among adults and adolescents with asthma to inform the development of the Asthma Daily Symptom Diary (ADSD)

## Methods

- This study followed the recommended PRO development process described in the FDA Guidance for Industry titled "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" (aka PRO Guidance)

Figure 1. Methods Flow Chart



## Literature Review

- A literature review was conducted to: 1) understand qualitative work conducted to date among asthma patients and 2) understand currently available asthma PRO measures<sup>1</sup>

## Conceptual Framework Development

- The conceptual framework was informed by the literature review described above, as well as information made available to the WG from a previously conducted literature review and focus groups related to asthma control

## Protocol Design

- The development of the protocol and semi-structured interview guide were based on the conceptual framework
- A panel of asthma experts reviewed the draft study protocol and provided input into the study design, including the target population and key demographic and clinical characteristics

## Concept Elicitation

- Initial discussions with participants were broad and open-ended in an effort to facilitate spontaneous reporting of symptoms; specific probes were only used once participants had been given every opportunity to elicit concepts spontaneously
- The symptoms experienced by participants and the features/attributes of these symptoms (e.g., frequency, intensity, duration) were the primary focus of exploration
- Factors which may contribute to the triggering or worsening of a symptom and the resulting impacts of symptoms were also considered

## Analysis of Qualitative Work

- A Qualitative Analysis Plan (QAP) was developed *a priori*
- The QAP defined the coding process, means of evaluating conceptual saturation, subgroup analysis and presentation of results
- All interview data was tape-recorded, transcribed verbatim and entered into ATLAS.ti
- Each transcript was assessed and participant comments that pertain to the main research questions were highlighted in accordance with an agreed coding scheme
- Conceptual saturation (i.e. that no new concepts emerged with continued data collection) was evaluated
- In addition, Adelphi Values (the WG's contract research partner) conducted subgroup analyses to understand the experiences of asthma patients and the relevance of elicited concepts among participants categorized according to age, levels of asthma control, recent history of exacerbations, type of medication used, gender, race, and ethnicity

## Item Generation

- Upon completion of the qualitative analyses, an item generation meeting was held among members of the Asthma Working Group, Adelphi Values, and the scientific advisors
- Results of the concept elicitation interviews were discussed; items were drafted which reflected how patients described symptoms in their own words

## Results

### Patient Sample

- Fifty-five interviews were conducted by trained AV interviewers at four centers across the US: New Orleans, Los Angeles, Philadelphia, and Pittsburgh; patient demographic and clinical characteristics met pre-defined quotas ensuring adequate inclusion of a diverse patient group

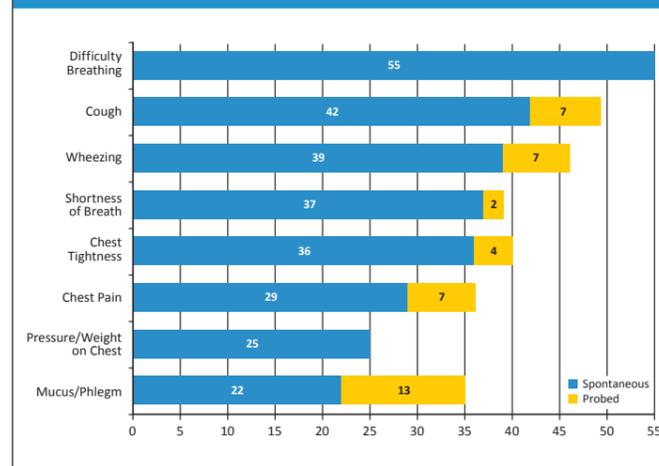
Table 1. Participant Demographics and Clinical Characteristics (n=55)

	Age 12-14 years (n=12)	Age 15-17 years (n=13)	Age 18-45 years (n=16)	Age ≥46 years (n=14)	Total (n=55)
<b>Sample Demographics and Clinical Data</b>					
Age Mean	13	16	34	57	31
Min, Max	12, 14	15, 17	18, 45	46, 76	12, 76
Gender n (%)					
Male	9 (75)	6 (46)	4 (25)	6 (43)	25 (45)
Female	3 (25)	7 (54)	12 (75)	8 (57)	30 (55)
Ethnicity n (%)					
Hispanic or Latino (of any race)	2 (17)	2 (15)	5 (31)	1 (7)	10 (18)
Non-Hispanic or Latino	10 (83)	11 (85)	11 (69)	13 (93)	45 (82)
Race n (%)					
White	4 (33)	7 (54)	5 (31)	9 (64)	25 (45)
Black/African American	4 (33)	3 (23)	6 (38)	4 (29)	17 (31)
Multi-racial	1 (8)	0	4 (25)	0	5 (9)
Asian or Pacific Islander	1 (8)	1 (8)	0	0	2 (4)
Other	2 (17)	2 (15)	1 (6)	1 (7)	6 (11)
Asthma Control according to physician n (%)					
Well-controlled	5 (42)	4 (31)	2 (13)	6 (43)	17 (31)
Not well-controlled	5 (42)	7 (54)	11 (69)	8 (57)	31 (56)
Very poorly controlled	2 (17)	2 (15)	3 (19)	0	7 (13)
Asthma control according to patient score on Asthma Control Test n (%)					
Well-controlled (≥ 20)	5 (42)	3 (23)	2 (13)	6 (43)	16 (29)
Not well-controlled (16-19)	4 (33)	6 (46)	6 (38)	2 (14)	18 (33)
Very poorly controlled (≤ 15)	3 (25)	4 (31)	8 (50)	6 (43)	21 (38)
Experience of an exacerbation in the three weeks prior to screening according to physician n (%)					
No exacerbation	2 (17)	5 (38)	3 (19)	8 (57)	18 (33)
Moderate exacerbation	6 (50)	8 (62)	10 (63)	4 (29)	28 (51)
Severe exacerbation	4 (33)	0	3 (19)	2 (14)	9 (16)

### Patient-Reported Symptoms

- Eight symptoms emerged as 'core asthma symptoms' based on their frequency of spontaneous report, how bothersome they were to participants, and their clinical relevance (as determined by literature review, existing PRO measures of asthma symptoms, clinician input, and additional qualitative data available to the working group) (Figure 2; n=55)
- Core symptoms included 1) Breathing Symptoms: difficulty breathing, shortness of breath, and wheezing; 2) Chest Symptoms: chest tightness, chest pain, and pressure/weight on chest; and 3) Cough Symptoms: cough and mucus/phlegm

Figure 2. Frequency of Participants Reporting Core Asthma Symptoms



- In total, 70 distinct symptoms (8 core and 62 non-core) were reported by participants and the majority (90.0%) emerged within the first two sets of interviews (n=37/55), confirming conceptual saturation
- Of the 62 'non-core' symptoms, the most frequently mentioned were 1) those typically associated with commonly co-occurring allergies, 2) non-specific symptoms, or 3) those associated with known side-effects of existing asthma medications; consensus among the working group's clinical advisors indicated that none of these should be considered core symptoms of asthma

Table 2. Participant Quotes for 'Core' Asthma Symptoms

Concept	Example Patient Quote
Difficulty breathing	"The times I have gone to urgent care is because I've had, uh, the wheezing and the coughing, and I just can't breathe." (419-F-44-NWC)
Shortness of breath	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 ... (107-F-17-NWC)
Wheezing	"I – I get wheezing in the night." (416-F-36-VPC)
Chest pain	"It's like every time I breathe, there's a pain in my chest." (317-M-16-NWC)
Chest tightness	"And it feels like if my chest... it feels like it just started squeezing it and just getting tight, tight and just feels like – like n – air just not going through or nothing." (308-F-14-VPC)
Pressure/weight on chest	"Feels like something really heavy is on your chest, and you just can't breathe right." (104-F-39-WC)
Mucus/phlegm	"When you breathe, you can feel it just a little bit, uh, like – you know, like phlegm or something like that." (405-M-52-WC)
Cough	"Like I can't stop, like I'll start coughing and I just can't stop for like five minutes - like it'll just go and go" (404-F-15-WC)

### Saturation Analysis

- Conceptual saturation was demonstrated for the eight core symptoms across all of the 21 groups defined according to sub-quotas for age, gender, ethnicity, race, education, asthma control, history or recent exacerbations, and steps of medication

### Item Generation

- Core Items**
  - Eight items were developed to measure the 'core' asthma symptoms identified during concept elicitation
- Additional Items**
  - Due to clinical relevance and concept salience among participants, three items were included in the draft ADSD, as the development of standardized items would be helpful to investigators:
    - Nighttime awakenings
    - Relief medications
    - Impact on usual activities
  - Recall Period:** It was agreed that the severity of relevant symptoms would be assessed twice daily (morning and evening)
    - It was agreed that a diary completed twice within a 24-hour period would be the most rigorous option for the assessment of asthma symptoms
    - Twice-daily administration will allay potential concerns regarding recall bias associated with longer recall periods, particularly among adolescent respondents
    - The twice-daily diary would need to be concise in order to minimize responder burden

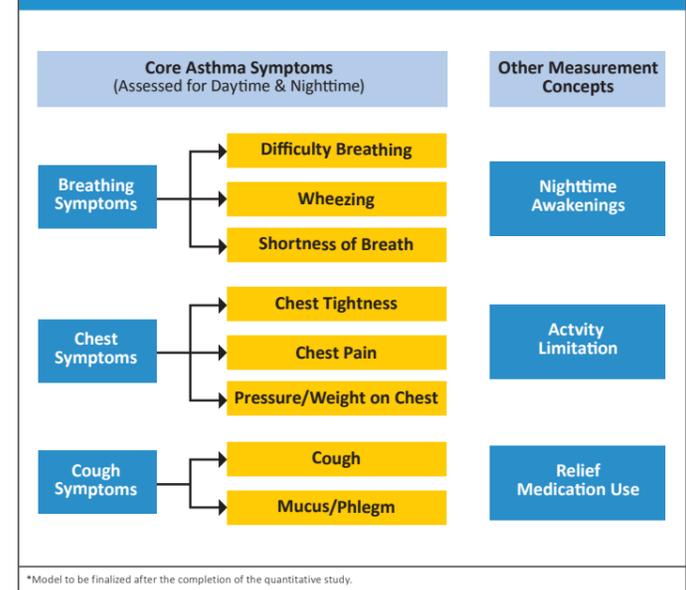
- Response Options:** Items were developed which asked respondents to rate each individual symptom at its 'worst' using a 0-10 numerical rating scale
  - Patients had spontaneously reported described symptom severity in this manner:

Table 3. Asthma Patients' Description of Symptoms

Symptom	Quote
Difficulty breathing	Q: "And how bad is – is your difficulty breathing? How bad would you say it is?" "It's like – it's in between – like, it would be, like, a five out of 10." Q: "How severe would you say that symptom is? How bad is it?... The can't breathe out." "Uh, like on a scale from one to 10, or you just want me to... On a scale from – one to 10, a 10."
Shortness of breath	Q: "How bad a symptom overall would you say that is, being short of breath?" "Uh, you want me – on a one to 10, or – "Sure. If you like." "OK. Well, short – being short, I'll say between a seven and eight. Because any time you're restricting your breathing – uh, you know, you – you've got a problem."
Wheezing	Q: "If – if you had to, you know, talk about your wheezing in terms of being bad or severe, how bad would you say wheezing is?" "Um, the wheezing, on a scale from one to 10, I'll give it about a six"

- Symptom Severity:** (as opposed to frequency, bothersomeness) was chosen based on patient descriptions of asthma symptom experience
  - Assessment of frequency is likely to be negated by daily assessment
  - Bothersomeness is not a well-defined concept, as it encompasses elements of frequency, severity, and impact; it would, therefore, not be robust enough to support an FDA labeling claim

Figure 3. Revised Hypothesized Conceptual Framework\*



## Conclusion

- The Asthma Daily Symptom Diary is a new PRO measure based on patients' direct experiences of asthma
- The Asthma Daily Symptom Diary as developed, may potentially support product labeling claims related to reduction of symptom severity or of symptom free days over a study interval
- Future research will involve testing the draft items to ensure that adolescents and adults with asthma find them relevant, understandable, and comprehensive

## References

- Nelsen LM, Gater A, Hall R, Coons SJ on behalf of the Critical Path Institute PRO Consortium Asthma Working Group. Identifying and Measuring the Core Symptoms Reported by Persons with Asthma: A review of the Existing Qualitative Literature and Patient-Reported Outcome Measures. Poster Discussion at: American Thoracic Society International Conference, May 16-21, 2014, San Diego, California.