Pediatric Asthma Working Group

12th Annual PRO Consortium Workshop – Held Virtually on April 14-15, 2021

Background

Rationale for Pediatric Asthma Working Group (WG)

- Pediatric asthma has been identified as an area in need of novel clinical outcome assessments (COAs) for evaluating clinical benefit in treatment trials.
- The Asthma Working Group (WG) has developed two patient-reported outcome (PRO) measures (i.e., *Asthma Daytime Symptom Diary* [*ADSD*], *Asthma Nighttime Symptom Diary* [*ANSD*]) for assessing asthma symptom severity in adolescents and adults.
- The U.S. Food and Drug Administration (FDA) requested that the Asthma WG consider developing COAs to cover a broader range of asthma patients (i.e., < 12 years old).
- Merck Sharpe & Dohme Corp. (Merck), a sponsor of the Asthma WG, contributed draft versions of a PRO measure (for completion by children ages 8 through 11 years old) and an observer-reported outcome (ObsRO) measure (for completion by parents or caregivers of children ages 4 through 11 years old) developed for use in pediatric asthma trials.
- Merck completed the qualitative phase of development of the two measures including concept elicitation and cognitive interviews with the respective target populations. Merck also received feedback from FDA on the draft measures.
- A separate Pediatric Asthma WG was formed to examine Merck's research and assess the adequacy of the two draft measures as candidates for qualification.

Goal of the Pediatric Asthma WG

- To pursue FDA qualification of measures for the assessment of asthma signs and symptoms in pediatric asthma treatment trials: the primary measure would be the *Pediatric Asthma Diary-Observer* (*PAD-O*), an ObsRO measure for parents/caregivers of the entire age range (4 through 11 years old). The observer would also consider input from other informants (e.g., siblings, teachers, babysitters, spouses) regarding observable asthma signs or impacts. The *Pediatric Asthma Diary-Child* (*PAD-C*), a PRO measure for children 8 through 11 years old, would be a supportive measure.

Targeted Labeling Language

- Patients treated with [*Drug X*] experienced a significant reduction in severity of asthma signs and symptoms.

Milestones

Milestone	Target Date	Completed Date
Reanalysis of Merck's pediatric qualitative data to identify gaps suggested by FDA that required additional research		SEP 2016
Letter of Intent submission to FDA		DEC 2016
FDA Response to Letter of Intent and request for Initial Briefing Package (IBP) received		MAY 2017
Feasibility study protocol submission to FDA		AUG 2017
Written feedback from FDA on protocol recommending separate ObsRO and PRO measures instead of co-completion		MAY 2018
Complete qualitative research on modified COA measures and cognitive interview study report submission to FDA	SEPT 2021	
Initial Briefing Package submission to FDA	MAR 2022	
Qualification Plan submission to FDA	TBD	
Full Qualification Package submission to FDA	TBD	

Highlights

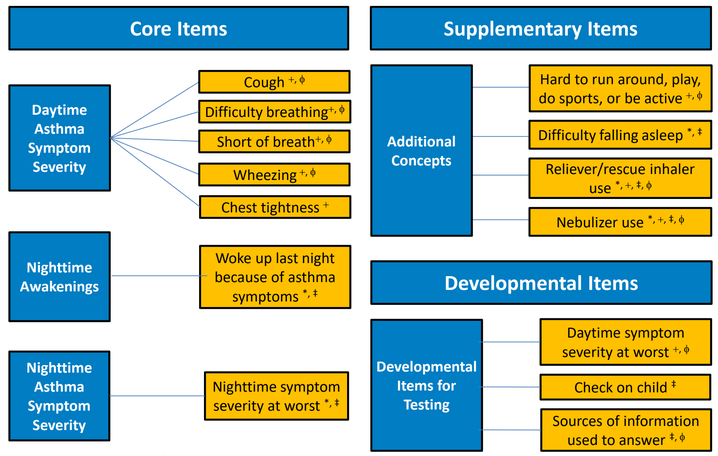
Example Endpoint Model for Treatment of Pediatric Asthma

Endpoint Hierarchy	Endpoint Concept(s)	Endpoint Type
Primary	Improvements in airflow obstruction • FEV_1 Reduction in asthma signs and symptoms	PerfO ObsRO (*PAD-O*)
Secondary	Proportion of days without asthma signs or symptoms Proportion of days without asthma signs or symptoms	ObsRO (*PAD-O*) PRO (*PAD-C*)

Target Population

- Children 4 through 11 years old with a clinical diagnosis of mild to severe persistent asthma requiring a daily long-term control medication.

Conceptual Framework



Item is included in the following measures:
* *PAD-C* (Morning Diary); + *PAD-C* (Bedtime Diary); ‡ *PAD-O* (Morning Diary); ϕ *PAD-O* (Evening Diary)

ObsRO measure: *Pediatric Asthma Diary-Observer (PAD-O)*

Core Items: Morning diary with 2 items and evening diary with 4 items
Recall Period: Morning diary: parent/caregiver-completed after child wakes up in the morning, thinking about the previous night since bedtime; evening diary: parent/caregiver-completed at child's bedtime, thinking about today since the child woke up in the morning
Response Options: 5- or 6-level verbal rating scale; Yes/No/I don't know
Symptom Attribute: Intensity or frequency as a measure of severity
Data Collection Mode: Electronic diary, likely handheld device

PRO measure: *Pediatric Asthma Diary-Child (PAD-C)*

Core Items: Morning diary with 2 items and bedtime diary with 5 items
Recall Period: Morning diary: self-completed upon waking up in the morning, thinking about the previous night since bedtime; evening diary: self-completed at bedtime, thinking about today since waking up in the morning
Response Options: 4- or 5-level verbal rating scale; Yes/No
Symptom Attribute: Intensity or frequency as a measure of severity
Data Collection Mode: Electronic diary, likely handheld device

Working Group Activities

Completed Activities

- FDA Broad Agency Announcement (BAA) contract executed on September 30, 2019, for project titled: Developing Novel Clinical Outcome Assessments for Pediatric Asthma to Facilitate Innovative Patient-Focused Drug Development and Aid Regulatory Decision Making.
- Advisory panel teleconference held February 19, 2020, to obtain input from clinician and parent representatives on the measures and the study design. Written feedback received from FDA in parallel.
- Cognitive interview study document preparation is complete. Study protocol, appendices, and consent/assent forms were IRB-approved in March 2020 and received "Not Engaged" determination from FDA on April 27, 2020.
- Round 1 cognitive interviews with 5 children and 10 parents/caregivers were conducted between October 13 and November 17, 2020.
- Round 2 cognitive interviews with 5 children and 10 parents/caregivers (independent of Round 1) were conducted between February 3 and March 11, 2021.

Unique Issues for the Working Group

- The age range for this target population is particularly challenging because of the wide range in cognitive development, ability to reliably report symptoms and understand timeframes (e.g., last night; since you woke up this morning), and ability to read and understand the diary items on their own for children between 8 and 11 years old.
- In addition, asthma is a symptomatic condition for which key symptoms such as chest tightness are not easily observed by others and therefore rely heavily on self-report.
- Concerns about complete, consistent coverage of asthma symptoms for younger ages led to use of Merck's draft ObsRO (for all ages) and PRO measures (for older children).
- Recommendations for use of the self-reported PRO measure for children 8 through 11 years old will allow the child's voice to be heard.
- Limitations of observability will be addressed by allowing the observer to incorporate what the child has said about symptoms as well as input from other informants (e.g., siblings, teachers, babysitters, spouses) regarding observable asthma signs and impacts.
- Instructions have been drafted for the observer to follow when completing the ObsRO measure to standardize the observer-reported process across respondents.
- COVID-19 has impacted cognitive interviews with children and parents/caregivers, which were planned to be conducted face-to-face for optimal results. This was not possible in Spring and Summer 2020 for the safety of participants and interviewers.
- C-Path has received a 1-year extension on the BAA contract in order to mitigate the COVID-19 delay. Due to the ongoing pandemic, the WG proceeded with web-based interviews via Microsoft Teams in September 2020 as an alternative to face-to-face interviews.

Next Steps

- The second advisory panel meeting is scheduled for April 7, 2021, to review results of Round 2 interviews and decide on changes to the measures.
- Round 3 cognitive interviews will be conducted from May through June 2021.
- The cognitive interview study report will be submitted to FDA by September 2021.

Working Group Participants

Company/Organization	Representatives
AstraZeneca AB	Erin Tomaszewski, PhD; Vivian Shih, DrPH
GlaxoSmithKline, LLC	Claire Trennery, MSc; Linda Nelsen, MHS
Research Partner	**Research Team**
Adelphi Values Patient-Centered Outcomes	Rob Arbuckle, MSc, MA; Rebecca Hall, MMedSci; Helena Bradley, BSc; Amy Jones, MSc; Aoife Lydon, MSc; Frances White, BSc