Pediatric Asthma Working Group

14th Annual PRO Consortium Workshop – Silver Spring, MD – April 19-20, 2023

PRO CONSORTIUM
CRITICAL PATH INSTITUTE

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 2 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 8 through 11 years old) and an observer-reported outcome (ObsRO) measure (for completion by parents or caregivers of children 4 through 11 years old) developed for use in pediatric asthma trials.
- Merck completed the qualitative phase of development of the 2 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 2 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., the child, 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, could be a supportive measure.

Targeted Labeling Language

- A greater proportion of patients 4 through 11 years old receiving [*Drug X*] experienced a clinically meaningful 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 COAs and cognitive interview study report submission to FDA		SEP 2021
Initial Briefing Package submission to FDA		MAR 2022
Qualification Plan submission to FDA		DEC 2022
Full Qualification Package submission to FDA	TBD	

Highlights

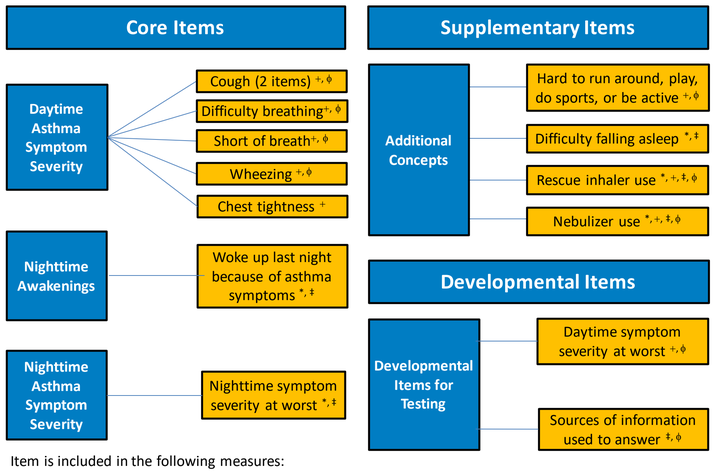
Example Endpoint Model for Treatment of Pediatric Asthma

Endpoint Hierarchy	Endpoint Concept(s)	Endpoint Type
Primary	Improvements in airflow obstruction • FEV_1 Reduction in severity of 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 Proportion of rescue medication free days	ObsRO (*PAD-O*) PRO (*PAD-C*) ObsRO (*PAD-O*)

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 5 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 smartphone-type device

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

Core Items: Morning Diary with 2 items and Bedtime Diary with 6 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 smartphone-type 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.
- Three rounds of cognitive interviews with 15 children and 30 parents/caregivers were conducted between October 13, 2020, and July 9, 2021.
- The second advisory panel meeting was held on April 7, 2021, to review results of Round 2 interviews and decide on changes to the measures.
- The cognitive interview study report was submitted to FDA on September 30, 2021.
- The Initial Briefing Package and User Manual were submitted to FDA on March 31, 2022.
- The third advisory panel meeting was held October 14, 2022, to obtain input on the study design, protocol, and related materials for the upcoming quantitative pilot study.
- The Qualification Plan (QP) was submitted to FDA on December 15, 2022, and FDA issued the Reviewability Memorandum on March 30, 2023, deeming the QP reviewable.
- A qualitative manuscript was submitted to *Journal of Patient-Reported Outcomes* on December 20, 2022, and is under review.

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.
- 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.
- The working group decided to allow multiple observer completion by a maximum of 2 caregivers to provide greater flexibility and inclusivity of a broader range of family circumstances. The working group will need to address challenges of this approach, including operationalizing it when conducting a study and defining a study design that will enable testing of multiple-observer agreement to confirm concordance between multiple observers within the context of a quantitative pilot study.

Next Steps

- FDA will conduct review of the QP.

Working Group Participants

Company/Organization	Representatives
AstraZeneca AB	Erin Tomaszewski, PhD; Vivian Shih, DrPH
GSK	Claire Trennery, MSc; Linda Nelsen, MHS
Research Partner	**Research Team**
Adelphi Values Patient-Centered Outcomes	Rob Arbuckle, MSc, MA; Rebecca Williams-Hall, MMedSci; Helena Bradley, BSc; Amy Jones, MSc; Aoife Lydon, MSc; Frances White, BSc; Asha Lehane, MSc; Menita Asriah, MSc; Jan Stochl, PhD; George Skingley, BSc; Rebekah Tyler-Brough, BSc