Pediatric Asthma Working Group

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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 assessment (COA) tools 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 COA tools 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 to 11 years old) and an observer-reported outcome (ObsRO) measure (for completion by parents or caregivers of children ages 4 to 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.
- The Asthma WG decided to focus its efforts on FDA qualification of the *ADSD* and *ANSD,* so 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 the measures for the assessment of asthma signs and symptoms in pediatric asthma treatment trials: the primary measure would be the ObsRO measure for parents/caregivers of the entire age range (4 to 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 PRO measure for children age 8 to 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 qualitative data to evaluate data and identify gaps suggested by FDA that required additional research		SEP 2016
Letter of Intent submitted to FDA		DEC 2016
Review documentation, recommendations for changes to the measure and recommendations for future research		FEB 2017
FDA Response to Letter of Intent and request for Initial Briefing Package (IBP) received		MAY 2017
Feasibility study protocol submitted to FDA		AUG 2017
Written feedback from FDA on protocol recommending separate ObsRO and PRO measures instead of co-completion		MAY 2018
Request for proposal (RFP) and vendor selection process	In progress	
Complete qualitative research on modified COA measures	TBD	
Submit Initial Briefing Package to FDA	TBD	
Submit Qualification Plan to FDA	TBD	
Submit Full Qualification Package to FDA	TBD	

Highlights

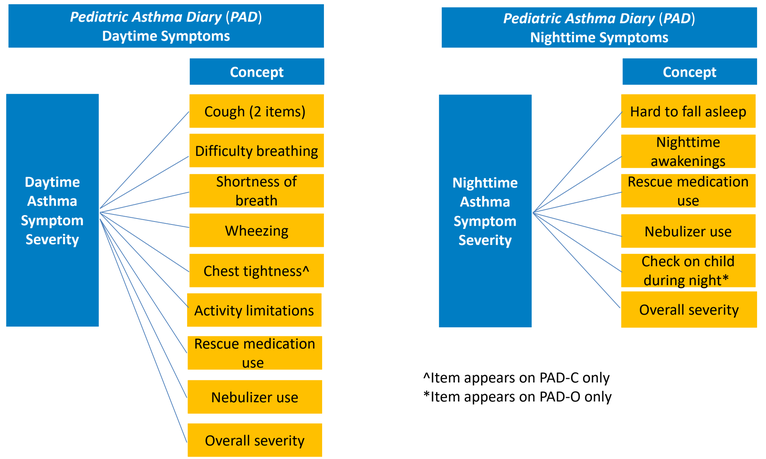
Example Endpoint Model for Treatment of Pediatric Asthma

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	ObsRO (*PAD-O*)

Target Population

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

Hypothesized Conceptual Framework



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

Core Items: Morning diary with 9 items and evening diary with 12 items
Recall Period: Morning diary: parent-completed upon the child waking up in the morning, thinking about the previous night since bedtime; evening diary: parent-completed at the child's bedtime, thinking about today since waking up in the morning
Response Options: 5- or 6-level verbal rating scale, Yes/No, and open responses
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 7 items and evening diary with 12 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, and open responses
Symptom Attribute: Intensity or frequency as a measure of severity
Data Collection Mode: Electronic diary, likely handheld device

Working Group Activities

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.
- 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 and consistent coverage of asthma symptoms for younger ages led to use of Merck's draft ObsRO (for all ages of children) and PRO measures (for older children).
- Recommendations for use of the self-reported PRO measure for children ages 8 to 11 years old and the ObsRO measure to be completed by parents (for children ages 4 to 11 years old) are being considered to allow the child's voice to be heard.
- The approach used in the Merck research may be problematic because of the limitations of observability of nighttime symptoms (as parents would also be sleeping) and of daytime symptoms (because parents may not be with the child for enough time during the day to reliably report their observations).
- These limitations 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.
- May be necessary to develop four measures to separate daytime and nighttime observations for both the PRO measure and the ObsRO measure.
- Continue to explore alternatives for assessing sleep/nighttime awakenings (e.g., actigraphy)

Next Steps

- Both measures are ready to be evaluated in cognitive interviews to determine if the modifications to wording, response options, and instructions are well understood by the respective target populations.
- Proposals were received in response to an RFP associated with the additional qualitative research needed to support the development and submission of an Initial Briefing Package.
- The chosen CRO will complete a study of approximately 45 participants to further evaluate the content validity of the measures.
- After completion of the qualitative research, an Initial Briefing Package will be submitted to FDA.

Working Group Participants

Company/Organization	Representatives
AstraZeneca AB	Sean O'Quinn, MPH
GlaxoSmithKline, LLC	Robyn Von Maltzahn, MSc
Novartis Pharmaceuticals	Note: Novartis provided initial funding but is no longer an active participant in the WG.
Contract Research Organization	**Research Team**
TBD	TBD