Asthma Working Group

Presented at the Tenth Annual PRO Consortium Workshop – Silver Spring, MD – April 24-25, 2019

PRO CONSORTIUM CRITICAL PATH INSTITUTE

Background

Rationale for Asthma Working Group (WG)

- Asthma was identified as an area for development of a novel PRO measure to support clinical trials. There is no standard PRO instrument that is qualified by FDA for the purpose of measuring important symptoms of asthma.
- The Asthma WG is working to address this unmet need within FDA's COA Qualification Program by developing a PRO instrument for use in clinical trials of asthma therapies in accordance with the FDA PRO Guidance.

Goal of the Asthma WG

- To develop a patient-reported diary to document daily asthma symptoms in adults and adolescents with a clinical diagnosis of mild to severe persistent asthma for use in clinical trials of asthma therapies as a co-primary or secondary endpoint measure to establish treatment benefit.

Targeted Labeling Language

- Among patients treated with [Drug X] compared to [Drug Z] over y weeks of treatment, patients treated with [Drug X] reported significant reductions in asthma symptom severity.
- Significantly more patients treated with [Drug X] reported improvements in asthma symptom severity.
- Patients treated with [Drug X] reported significantly fewer days with asthma symptoms.
- Patients treated with [Drug X] reported a significantly higher number of symptom free days.

Milestones

Milestone	Expected Date	Completed Date
Vendor selection and contracting		FEB 2012
Complete background research (Literature Review Report and Expert Panel Meeting)		SEP 2012
Draft Instrument: Complete initial qualitative research and generate items (concept elicitation interviews, item generation, expert panel input, and initial round of cognitive interviews)		AUG 2013
Submit Qualitative Research Summary Briefing Document to FDA for review and feedback		NOV 2013
Complete quantitative pilot study		OCT 2015
Complete data analysis and Quantitative Pilot Study Report		OCT 2016
Submit Qualification Briefing Package to FDA for exploratory use of *ADSD*		DEC 2016
Complete revised Quantitative Pilot Study Report incorporating reanalysis of *ADSD* with 6 instead of 7 items (mucus/phlegm item removed at FDA request)		OCT 2017
Submit Full Qualification Package for 6-item *ADSD*		MAY 2018
Submit revised User Manual and renamed measures *(ADSD/ANSD)* to FDA		JAN 2019
Qualification statement issued for use of *ADSD/ANSD*		MAR 2019

Highlights

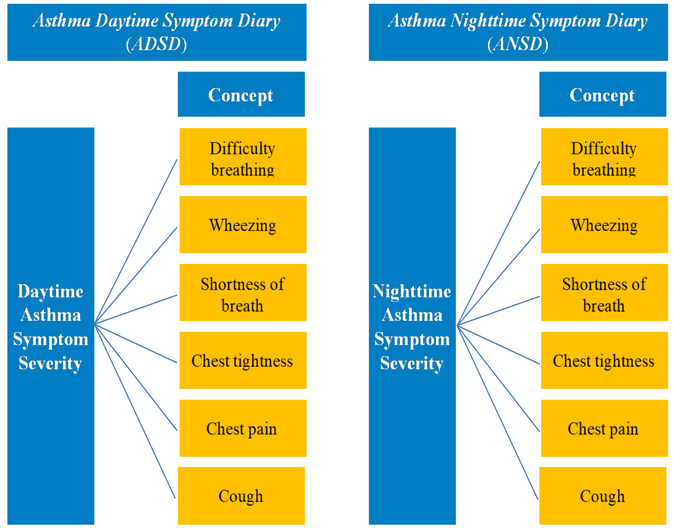
Example Endpoint Model for Treatment of Asthma

Endpoint Hierarchy	Endpoint Concept(s)	Endpoint Type
Primary	Improvements in airflow obstruction • FEV_1 Reduction in asthma symptoms	PerfO PRO (*ADSD/ANSD*)
Secondary	Proportion of days without asthma symptoms based on symptom free days	PRO (*ADSD/ANSD*)

Target Population

- Adolescents and adults aged 12 years and older with a clinical diagnosis of asthma with lung function impairment
- Patients across guideline-defined levels of disease severity, which include mild through severe persistent asthma (GINA, 2009)

Conceptual Frameworks



Measures – *Asthma Daytime Symptom Diary* (*ADSD*) *Asthma Nighttime Symptom Diary* (*ANSD*)

Core Items: Six items all leading to an asthma symptom severity domain for each measure

Recall Period: *ADSD* is to be completed in the evening and asks about daytime symptoms and *ANSD* is to be completed in the morning and asks about nighttime symptoms.

Response Options: 11-point numeric rating scale

Symptom Attribute: Severity was chosen based on patient descriptions of asthma symptom experience.

Data Collection Mode: Handheld smartphone device used for quantitative pilot study

Working Group Activities

Completed Activities

- Quantitative Pilot Study Report and quantitative data submitted to FDA in October 2016
- Qualification Briefing Package submitted to FDA in December 2016
- At FDA request, mucus/phlegm item removed and reanalysis performed on 6-item measure
- Revised Quantitative Pilot Study Report submitted to FDA in October 2017
- Revised Full Qualification Package submitted to FDA in May 2018
- A revised User Manual, including both *ADSD* and *ANSD,* submitted to FDA in January 2019

Information Dissemination

- Gater A, Nelsen L, Fleming S, et al. Assessing asthma symptoms in adolescents and adults: Qualitative research supporting development of the Asthma Daily Symptom Diary. *Value in Health* 2016;19(4): 440-450.
- A manuscript reporting the results of the quantitative pilot study will be prepared for submission to a clinical journal following qualification of the *ADSD* and *ANSD.*

Unique Issues for the Working Group

- The Item Refinement Meeting held in January 2016 resulted in a 7-item measure that was agreed to by WG, Expert Panel, and FDA representatives, and quantitative analysis was conducted accordingly.
- FDA subsequently requested reduction to a 6-item measure, which required revision and resubmission of key deliverables.
- In December 2018, the morning and evening diary components of the original *ADSD* were renamed *Asthma Daytime Symptom Diary* and *Asthma Nighttime Symptom Diary* to reduce ambiguity and to be more intuitive than the previous Morning Diary and Evening Diary designations. They are separate measures that are scored independently and may be used separately or together based on the sponsor's study design.

Next Steps

- Several WG sponsor clinical trials using the *ADSD*/*ANSD* are underway.
- A manuscript documenting the cross-sectional measurement properties is being developed.

Working Group Participants

Company/Organization	Representatives
AstraZeneca AB	Niklas Karlsson, PhD; Sean O'Quinn, MPH
Boehringer Ingelheim	Mike Baldwin, MBA
Allergan	Robyn T. Carson, MPH
Genentech, Inc.	Alison Greene, MPH; Alison Matsui, MPH
GlaxoSmithKline, LLC	Linda Nelsen, MHS, Robyn von Maltzahn, MSc.
Janssen Global Services, LLC	Chenglong Han, MD, PhD
Merck Sharp & Dohme Corp.	Josephine Norquist, MS
Novartis Pharma AG	Denise D'Alessio, MBA
Pfizer, Inc.	Note: Pfizer funded but is no longer a participant in the working group
Sanofi	Asif Khan, MBBS, MPH; Laurent Eckert, PhD, MS
Expert Panel Members	**Affiliation**
Michael Schatz, MD	Kaiser Permanente, UCSD
Jerry Krishnan, MD, PhD	University of Chicago, NHLBI
John Haughney, MB	University of Aberdeen
Stuart Stoloff, MD	Fellow FAAAAI, Family Practitioner
Contract Research Organization	**Research Team**
Adelphi Values	Adam Gater, MSc; Rob Arbuckle, MSc; Nicola Bonner, MSc; Rebecca Hall, MMedSci;
ePRO System Provider	**Representative**
CRF Health	Paul O'Donohoe, BSc (at the time of the study)