The Asthma Working Group

On the Path to Success

SIXTH ANNUAL

PATIENT-REPORTED OUTCOME CONSORTIUM WORKSHOP

April 29 - 30, 2015 ■ Silver Spring, MD
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Session Participants

Moderator
– Josephine Norquist, Patient-Reported Outcomes Specialist, Merck, Sharp & Dohme Corp

Presenters and Panelists
– Linda Nelsen, Director, Patient Focused Outcomes, GlaxoSmithKline
– Adam Gater, Director, Endpoint Development and Outcomes Assessment, Adelphi Values
– Elektra Papadopoulos, Acting Associate Director, Study Endpoints and Labeling Development, FDA
Objectives

Asthma Daily Symptom Diary (ADSD)

• Define need for standardized assessment of asthma symptoms in asthma treatment trials
• Describe how the structure of qualitative research informed the draft ADSD items, item structure, and response scale
• Describe how the quantitative pilot study will assess item and scale functioning
• Discuss FDA Response to ADSD Development and proposed quantitative study
• Discuss next steps in ADSD development
Background
Asthma Symptom Measurement

- Asthma symptoms are used to diagnose disease, monitor response to treatment and monitor disease control
- Existing asthma symptom measures are not standardized:
  - Often “homemade” instruments
  - Have poorly described development
  - Limited validation across the range of asthma target populations
- No adequately developed asthma symptom diary was identified in published literature
- Lack of standardized symptom assessment limits ability to
  - Interpret results of individual studies
  - Examine and compare outcomes across clinical studies and treatment
To develop a daily diary of asthma symptoms (for adolescents and adults) which:

- Uses methodology consistent with the FDA PRO guidance
- Can be used as co-primary or secondary endpoint in clinical research to:
  - Establish treatment benefit
  - Support product labeling claims
# Asthma WG Timelines

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Expected Date</th>
<th>Completed Date</th>
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</thead>
<tbody>
<tr>
<td>Scoping Stage</td>
<td>March 2010</td>
<td>Nov 2010</td>
</tr>
<tr>
<td>Content Validity Stage</td>
<td></td>
<td></td>
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<tr>
<td>Vendor selection and contracting</td>
<td>Jun 2011</td>
<td>Feb 2012</td>
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<tr>
<td>Background research</td>
<td>Jul 2012</td>
<td>Sept 2012</td>
</tr>
<tr>
<td>Draft instrument</td>
<td>Aug 2013</td>
<td>Aug 2013</td>
</tr>
<tr>
<td>Submit qualitative research summary briefing document</td>
<td>Oct 2013</td>
<td>Nov 2013</td>
</tr>
<tr>
<td>Submit updates to FDA (final cognitive interviews/report, updated ADSD, quantitative protocol)</td>
<td>Jun 2014</td>
<td>Jul 2014</td>
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</tbody>
</table>

- **Complete documentation of content validity and cross-sectional evaluation of other measurement properties**: T:2Q2015 → T:4Q2015
- **Submit exploratory endpoint qualification dossier to FDA**: T:3Q2015 → T:1Q2016
Asthma WG
Elements Supporting Success

• Defined, focused area of measurement
  – Asthma symptoms are well characterized and supported focused qualitative research

• Selection of valued expert consultants
  – Diligent selection process by full Asthma WG
  – Open-minded
  – Strong clinical experience
  – Expertise in conducting clinical trials
Asthma WG Context
Key Components Expressed by FDA

• Patient focused – face and content validity
• Diary design elements
  – Assess symptoms individually rather than globally
    • Aid interpretability and comprehensiveness of efficacy assessment
  – Short recall
    • Reduce recall bias and enhance reliability
• Ensure qualitative research covers entire target population
• Ease of translation
Asthma
Hypothesized Conceptual Framework

Daytime Asthma Symptoms
- Cough
- Wheeze
- Trouble breathing
- Chest tightness

Nighttime Asthma Symptoms
- Cough
- Wheeze
- Trouble breathing
- Chest-tightness
Elements of Qualitative Research

**Concept Elicitation**

- Qualitative literature review
- Reanalysis of existing qualitative data
- Concept elicitation interviews (n=55)

**Item Generation**

- Item generation meeting
- Translatability assessment
- ePRO migration assessment

**Cognitive Debriefing**

- Cognitive interviews (n=65)
- Evaluation of item response distributions and endorsement

**Quantitative Pilot Study**

- Analyses to evaluate item performance
- Determination of scoring
- Exit interviews (n=24)

**Clinical Trial Evaluation**

- Confirmation of reliability and validity of ADSD scores
- Evaluation of other measurement properties (incl. responsiveness and MID)
Qualitative Study: 
Need for Diverse Population

- Demonstrate **saturation for 4 age groups**
  - 12-14, 15-17, 18-45, 46+
- Quotas supported representation across demographic and clinical characteristics associated with asthma outcomes
  - **Gender:** Male -- Female
  - **Ethnicity:** Hispanic or Latino -- Non-Hispanic
  - **Race:** White -- Black/African American/Multi-racial/Other races
  - **Education:** High school or less -- College or higher
  - **Asthma control:** Well -- Not well -- Very poorly controlled
  - **Exacerbations:** Recent (e.g. past 3 weeks) -- No recent
  - **Medication use:** Asthma Guideline Steps: 1/2 -- Step 3/4-5/6
Overview of Symptoms: Core Symptoms

- 55 concept elicitation interviews
- 70 distinct symptoms were reported by participants
- 8 symptoms suggested as “core asthma symptoms”
  - Based on frequency of mentioned and clinical relevance
**Assessment of Symptom Experience/Severity**

- **Numeric Rating Scale (NRS) for assessment of symptom severity**
  - Intuitive to patients – participants frequently described symptoms on a 0 to 10 scale
  - Improved reliability and responsiveness/sensitivity to change at ends

Since you completed the diary [this morning/last night], rate your x when it was at its worst

**Option 1: Numeric Rating Scale (selected)**

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<thead>
<tr>
<th></th>
<th>0</th>
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<th>3</th>
<th>4</th>
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<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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<tbody>
<tr>
<td>0</td>
<td>None</td>
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<td></td>
<td></td>
<td></td>
<td>As bad as you can imagine</td>
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</table>

**Option 2: Verbal Rating Scale**

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<th>3</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>Not at all hard to breathe</td>
<td>A little hard to breathe</td>
<td>Somewhat hard to breathe</td>
<td>Very hard to breathe</td>
<td>Extremely hard to breathe</td>
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</tbody>
</table>

- **Focus on ‘worst’ symptom experience**
  - More reliable than reflection of “average “
  - More reflective of burden experienced by patients.
Markers of patient experience

- Overall endorsement: 39 (71%) participants discussed SOB
- Spontaneous mention: by 37 (95%)
- Most frequent: 27% versus 9% as least frequent symptom.
- Most bothersome: 28% versus 9% as least bothersome symptom.
- Worst symptom: reported by 17%

Concept relevance by demographic and clinical characteristics

- More commonly reported by ages 15-17 (85%) and 46+ (100%) vs. ages 12-14 (50%) and 18-45 (50%).
- More commonly reported among non-Hispanic (78%) than Hispanic participants (40%).
- Most commonly reported among patients on step 4/5 asthma medications (83%)

How experienced

- Frequency ranged from daily to once every couple of months
- Duration ranged from “10 seconds” to “all day”
- Intensity ranged from mild to severe
Thirty-five of the 39 participants (90.0%) used the term “shortness of breath” with 34 participants (97.1%) mentioning the term spontaneously.

<table>
<thead>
<tr>
<th>Terms used</th>
<th>Age Group (N)</th>
<th>Example quotes</th>
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<tbody>
<tr>
<td>“Shortness of breath” (n=35)</td>
<td>12-14 (4)</td>
<td>“Um, well, it’s just the wheezing, the shortness of breath, um, and then, I get – my nose, but no, other than that.” (F-17-NWC)</td>
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<td>15-17 (11)</td>
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<td>18-45 (7)</td>
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<tr>
<td></td>
<td>46+ (13)</td>
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<tr>
<td>“Catch my breath” (n=15)</td>
<td>12-14 (4)</td>
<td>“I can’t catch my breath at all.” (F-46-VPC)</td>
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<td>15-17 (2)</td>
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<td>18-45 (4)</td>
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<td>46+ (5)</td>
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<td>“Not getting enough air in” (n=6)</td>
<td>12-14 (2)</td>
<td>“I just – it seems like I can’t get enough air – and – I have to keep – just breathing in, just trying to take in air because I feel like I’m not getting enough.” (F-17-NWC)</td>
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<tr>
<td></td>
<td>15-17 (2)</td>
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<td>18-45 (1)</td>
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<td>46+ (1)</td>
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<tr>
<td>“Gasping” (n=5)</td>
<td>12-14 (2)</td>
<td>“It’s, like, you just – you’re out of breath. So you’re, like, gasping for air.” (M-14-WC)</td>
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<tr>
<td></td>
<td>15-17 (1)</td>
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<tr>
<td></td>
<td>18-45 (1)</td>
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<td></td>
<td>46+ (1)</td>
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NWC=Not well controlled; VPC=Very poorly controlled; WC=Well-controlled
Example

Shortness of Breath: Relevance

• **Is it important to assess shortness of breath?**
  • 71% mention this symptom; more commonly reported by more severe asthmatics
  • Considered if it was different from ‘difficulty breathing’ or ‘hard to breathe’?
    • Consider including and testing against difficulty breathing/hard to breathe
  • Frequency and severity equally mentioned by patients to describe the experience

• **How has shortness of breath been assessed previously?**

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Item</th>
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</table>
| Asthma Control Diary (ACD)                        | How much shortness of breath did you experience today?  
  0 = None; to 6 = A very great deal                  |
| Asthma Quality of Life Questionnaire – Marks      | I have been troubled by episodes of shortness of breath.  
  Version (AQLQ-Marks)                                | Not at all (0) to Very severely (5)                              |
| Lara Asthma Symptom Scale (LASS)                  | During the last 4 weeks, how often did your child have any of the following symptoms?  
  3. Shortness of breath?  
  1 = Never to 5 = Every day                          |
**Assessment of shortness of breath**

- Please rate your shortness of breath at its worst since you (got up this morning/went to bed last night)

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None | As bad as you can imagine
Asthma WG: *ADSD* Development

**Elements of Qualitative Research**

**Cognitive Debriefing**

- **Concept Elicitation**
  - Qualitative literature review
  - Reanalysis of existing qualitative data
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- **Item Generation**
  - Item generation meeting
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- **Quantitative Pilot Study**
  - Analyses to evaluate item performance
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  - Exit interviews (n=24)

- **Clinical Trial Evaluation**
  - Confirmation of reliability and validity of *ADSD* scores
  - Evaluation of other measurement properties (incl. responsiveness and MID)
Cognitive debriefing of ADSD
Item 3: Shortness of Breath

• **Relevance:**
  - 95.4% reported shortness of breath was relevant to their asthma experience.

• **Understanding:**
  - Participants used a variety of terms to describe the concept
  - “not getting enough air”, “frequency of exhalation and inhalation”, “panting/gasping for air”, “can’t catch breath”, “tightness”, “difficulty breathing” and “taking deep breaths”

• **Differentiating from other concepts:**
  - **Versus difficulty breathing:** 51.7% of participants reported shortness of breath and difficulty breathing as different symptoms.
  - **Versus wheezing:** 94.2% of participants thought shortness of breath and wheezing were different symptoms.

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**No Change: Recommended final shortness of breath item**

Please rate your shortness of breath at its worst since you (got up this morning/went to bed last night).
90.4% of participants felt that the use of the 11-point NRS was
- *Appropriate* to rate their asthma symptoms
- Easy to answer the items using this scale.

Understanding of NRS anchors
- Interpreted the term ‘*none*’ correctly (i.e. they did not experience the specified symptom at all in the specified time period)
- Provided explanations which demonstrated an understanding of the term ‘*as bad as you can imagine*’

Responses to *ADSD* items used the entire response continuum
- Limited responses at the upper end of the response continuum (8-10)
  - Not anticipated to have exacerbating patients at cognitive debriefing
- When asked to provide hypothetical ratings as to how bad symptoms could get, majority of participants said that a *10* would be the worst
When asked about the recall period, the FDA stated “we agree with the twice-daily reporting frequency and recall periods that you propose.”

In 209 cognitive debriefing instances, participants were asked about what time period they were thinking of when reading instructions or completing an item.

- In 74.6% of those instances, participants indicated a correct recall period

Participants thinking over an incorrect recall period were generally thinking beyond the time

- May be due to the context of the cognitive interviewing situation
- Will be further evaluated in exit interviews following quantitative pilot study
- Predominantly adolescents
Revised Conceptual Framework

**Core Asthma Symptoms**
(Assessed for Daytime & Nighttime)

- Difficulty breathing
- Wheezing
- Shortness of breath

**Breathing Symptoms**

**Chest Symptoms**

- Chest tightness
- Chest pain
- Pressure/weight on chest

**Cough Symptoms**

- Cough
- Mucus/phlegm

**Other Measurement Concepts**

- Night-time awakenings

**Activity Limitation**

**Relief Medication Use**
Overview of Quantitative Pilot Study: Objectives

- Designed to collect quantitative data to:
  - Support the content validity of the ADSD
  - Determine final instrument content
  - Inform development of scoring algorithms
  - Provide preliminary insight into ADSD measurement properties

Concept Elicitation
- Qualitative literature review
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Clinical Trial Evaluation
- Confirmation of reliability and validity of ADSD scores
- Evaluation of other measurement properties (incl. responsiveness and MID)
Quantitative Pilot Study: Design

- Participants complete the *ADSD* and concurrent measures over a 10-day study
- 200 participants targeted for recruitment: 80 adolescents (12-14yrs); 40 adolescents (15-17yrs); 40 adults (18-45yrs); 40 adults (46+yrs)
- Quotas to ensure demographically and clinically diverse population

<table>
<thead>
<tr>
<th>Data Collected</th>
<th>Schedule of Assessments</th>
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<tbody>
<tr>
<td></td>
<td>Screening</td>
</tr>
<tr>
<td>Case Report Form (Clinician)</td>
<td>X</td>
</tr>
<tr>
<td>Recruitment Screener (Recruitment agency)</td>
<td>X</td>
</tr>
<tr>
<td>Patient-Reported Data</td>
<td></td>
</tr>
<tr>
<td>Asthma Control Test (ACT)</td>
<td>X</td>
</tr>
<tr>
<td>Asthma Daily Symptom Diary (ADSD)</td>
<td>X X X X X X X X X X X</td>
</tr>
<tr>
<td>Patient Global Impression of Symptom Severity (PGI-S)</td>
<td>X X X X X X X X X X X</td>
</tr>
<tr>
<td>Patient Global Impression of Change (PGI-C)</td>
<td>X</td>
</tr>
<tr>
<td>Adult Asthma Symptom Diary Scales (AASDS)</td>
<td>X</td>
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</table>
Exit interviews

• Interviews to be conducted with study participants (n=24) to:
  – Explore usability of ePRO during at home completion
  – Ensure participant understanding of ADSD items
  – Understand differences in scores (day-to-day variation etc.)
  – Understand reasons for missing data

• A diverse population (with over representation of younger participants aged 12-14yrs) targeted for interview
Assessing *ADSD* item performance and scale structure

- Test-retest reliability
- Known-groups validity

Explore relationships between individual items
- Inter-item correlations
- Principal component / factor analysis

Evaluate participant responses to individual items
- Quality of completion
- Patterns of missing data
- Item response distributions (floor / ceiling effects, endorsement frequencies etc.)
- Differential item functioning

Assess the reliability and validity of individual items
From PRO items to scores: Key questions

• Can the *ADSD* be used to derive a total score?

• If items are combined to form a total score, how will responses on each item contribute to this score
  – E.g. (average response, sum total, maximum within a given domain, applied weighting)?

• How will items from the daytime and nighttime diary be combined and used to derive *ADSD* scores if at all?

• What is the timeframe over which scores should be derived (e.g. daily, weekly)?
Psychometric evaluation of ADSD scores

- **Internal consistency reliability**: To assess the homogeneity of items within the proposed groupings to ensure that the items are related but not redundant.

- **Test-retest reliability**: To assess the reliability of ADSD scores from day 3 to day 10 among “stable” subjects (i.e., defined by PGI-S and PGI-C).

- **Construct validity correlations**: To evaluate how well ADSD scores correlate with scales that measure similar concepts and scales that measure dissimilar concepts (i.e., convergent and discriminant validity).

- **Known-groups methods for construct validity**: To assess the extent to which ADSD scores are associated with patient’s known disease status and/or health status (e.g., asthma severity, level of control, history of exacerbations).
Revised Conceptual Framework:
Linking Measurement Concepts to Product Labeling Claims

- **Key measurement concepts:**
  - Daily symptom experience (daytime and nighttime symptoms)
    - To calculate symptom-free days
  - Daily symptom severity (daytime and nighttime symptoms)
    - To assess improvements/worsening in symptoms overtime
  - Nighttime awakenings
    - To calculate frequency of nighttime awakenings
  - Relief medication use (daytime and nighttime)
    - To understand if changes in symptom frequency or severity are due to changes in relief medication use.
    - To assess relief-free days
Future Steps

• Define and psychometrically validate specific endpoints derived from daily diary
  – Average weekly score versus Symptom free days
• Need for pediatric symptom measures
• Inclusion of *ADSD* for exploratory use in clinical trials across a range of
  – Asthma populations
  – Demographic groups
Discussion
Questions?
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