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

Goal of the PRO Consortium's Asthma Working Group

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

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

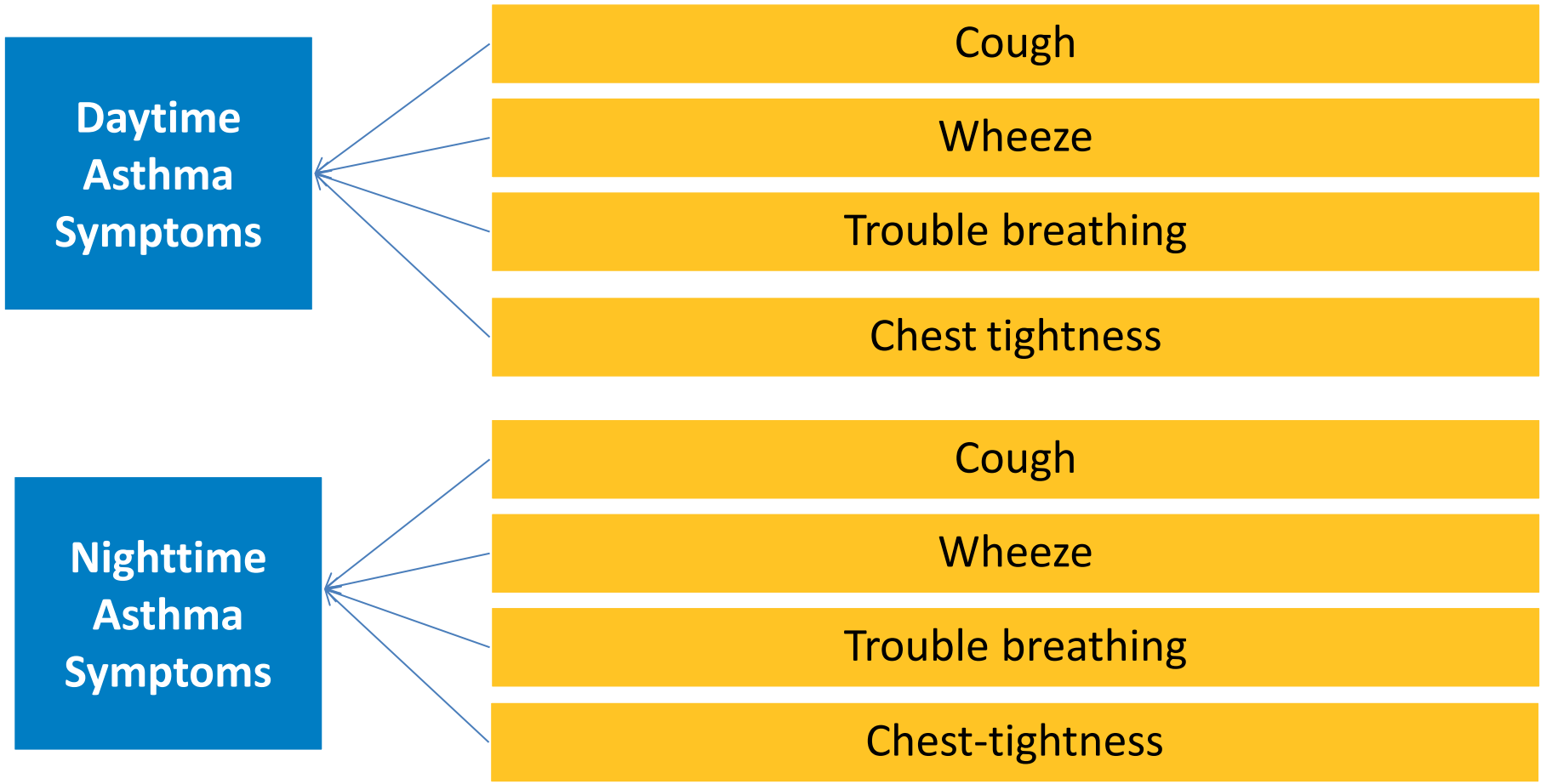
Asthma WG
Elements Supporting Success

- 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

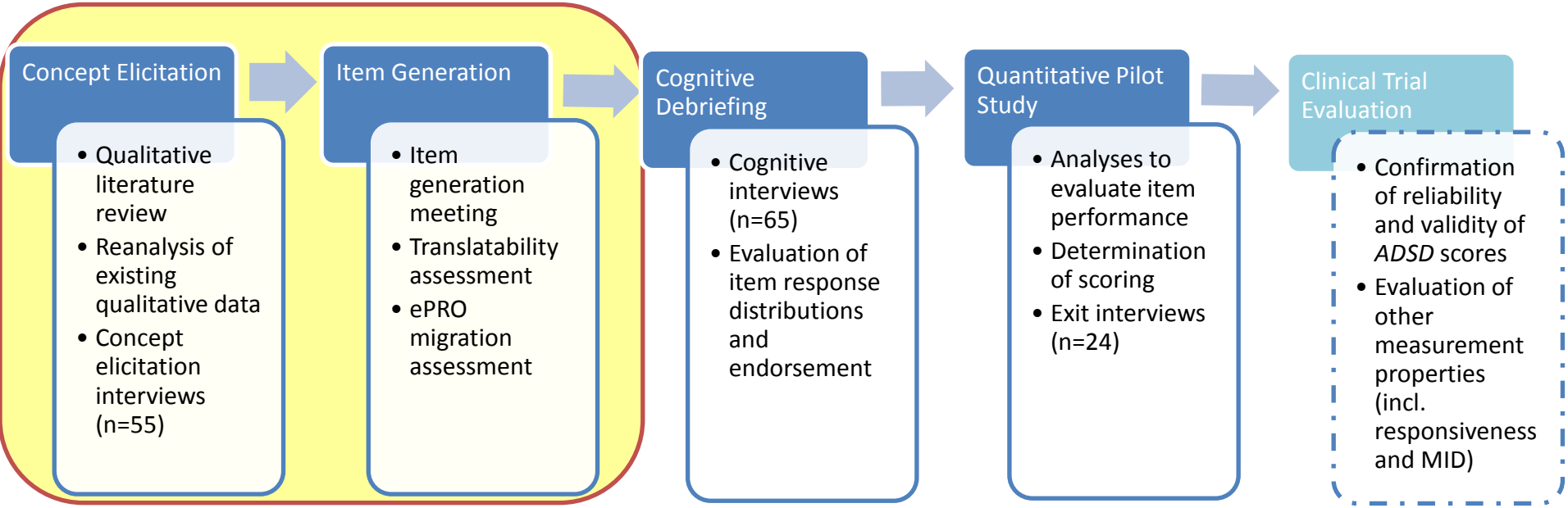


Asthma WG: *ADSD* Development

Elements of Qualitative Research

Concept Elicitation

Item Generation

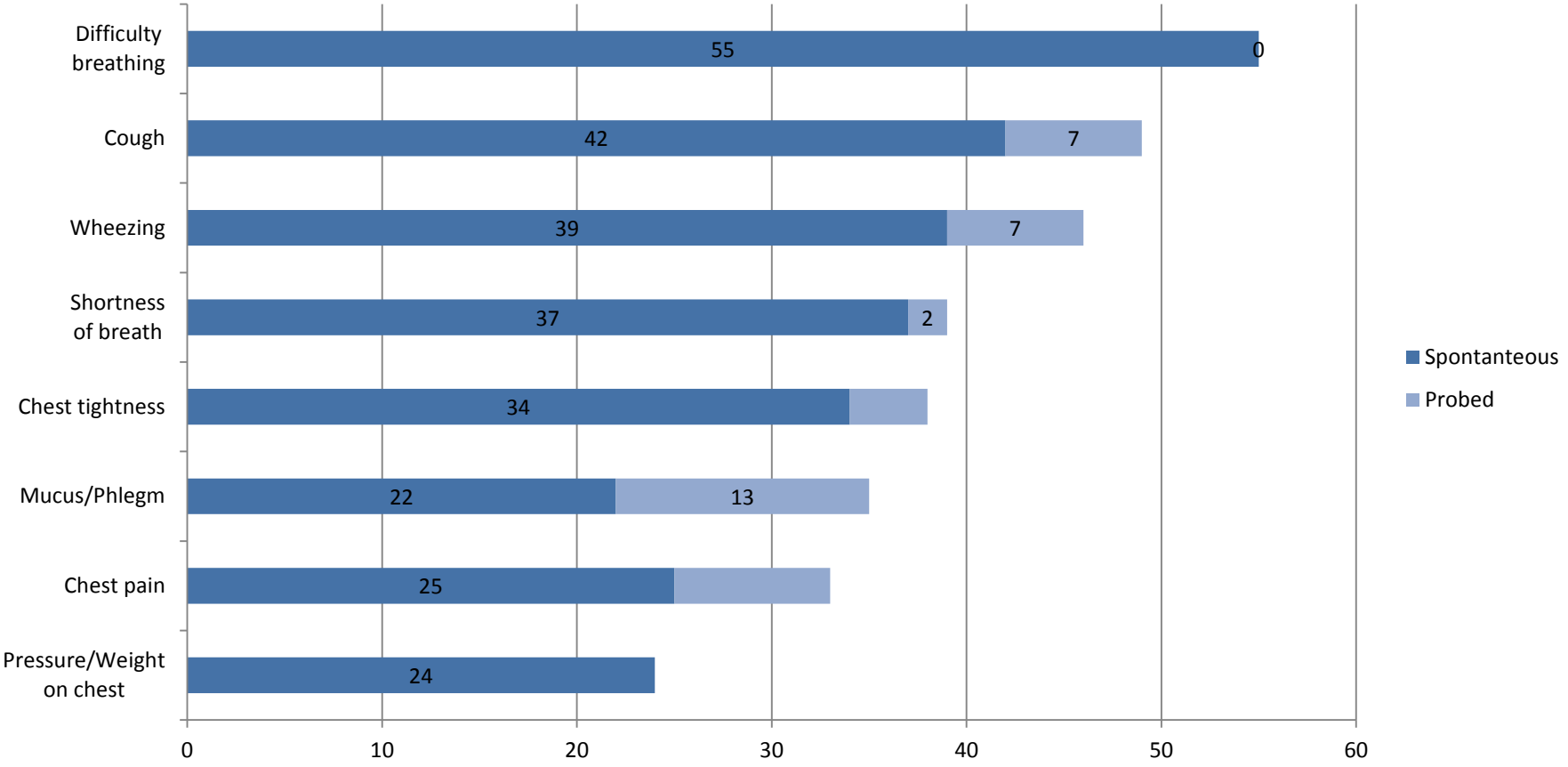


Qualitative Study: Need for Diverse Population

- 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

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- **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)

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as you can imagine**

Option 2: Verbal Rating Scale

0	1	2	3	4
Not at all hard to breathe	A little hard to breathe	Somewhat hard to breathe	Very hard to breathe	Extremely hard to breathe

- **Focus on 'worst' symptom experience**
  - More reliable than reflection of "average "
  - More reflective of burden experienced by patients.

Example
Shortness of Breath *(SOB)*

- **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

Shortness of Breath: Terms Used

- **Thirty-five** of the **39** participants **(90.0%)** used the term "shortness of breath" with **34** participants **(97.1%)** mentioning the term spontaneously

Terms used	Age Group (N)	Example quotes
"Shortness of breath" (n=35)	12-14 (4) 15-17 (11) 18-45 (7) 46+ (13)	"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)
"Catch my breath" (n=15)	12-14 (4) 15-17 (2) 18-45 (4) 46+ (5)	"I can't catch my breath at all." (F-46-VPC)
"Not getting enough air in" (n=6)	12-14 (2) 15-17 (2) 18-45 (1) 46+ (1)	"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)
"Gasping" (n=5)	12-14 (2) 15-17 (1) 18-45 (1) 46+ (1)	"It's, like, you just – you're out of breath. So you're, like, gasping for air." (M-14-WC)

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?**

Questionnaire	Item
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 Version (AQLQ-Marks)	I have been troubled by episodes of shortness of breath. 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

Example
Shortness of Breath: Draft *ADSD* Item

- **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)

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

Asthma WG: *ADSD* Development

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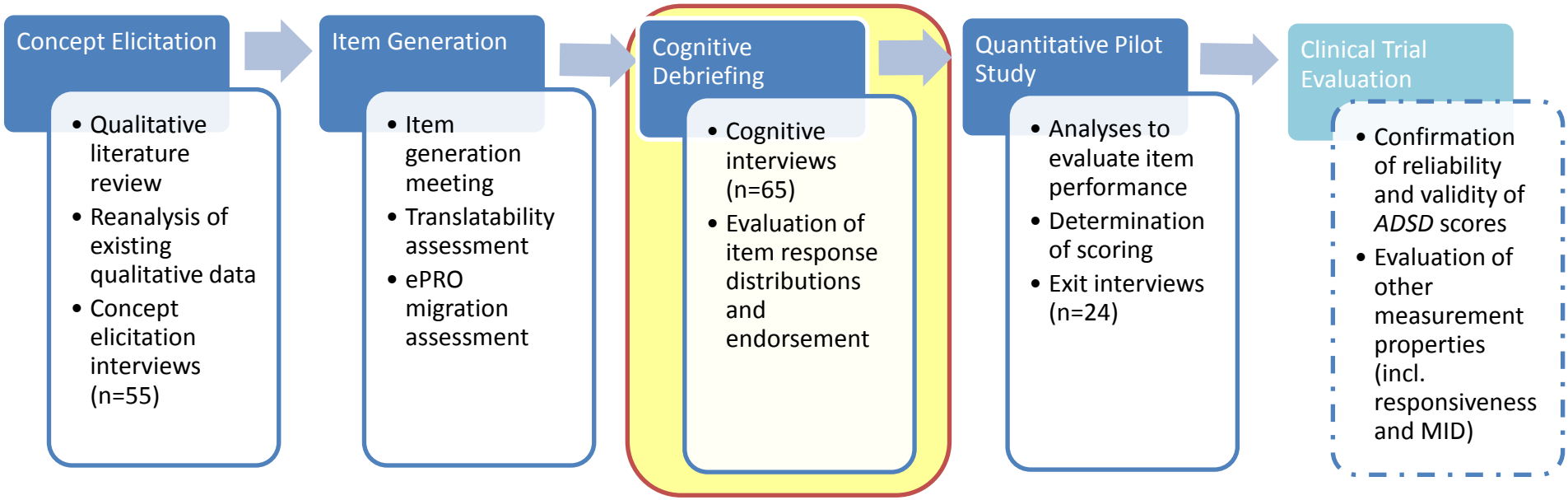
Elements of Qualitative Research

Cognitive Debriefing



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.

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).

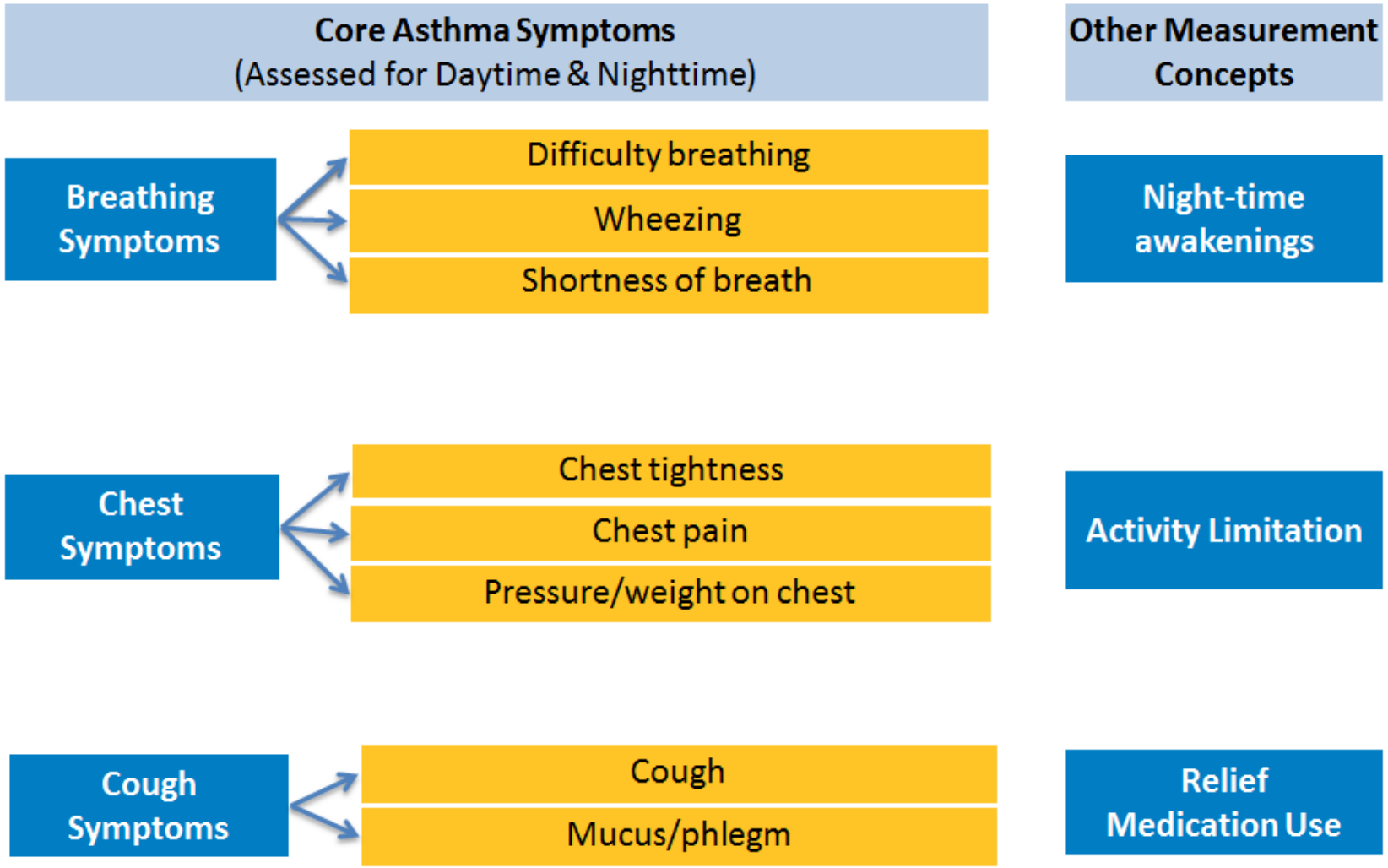
Response options: 11-point numeric rating scale (NRS)

- 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

Recall period

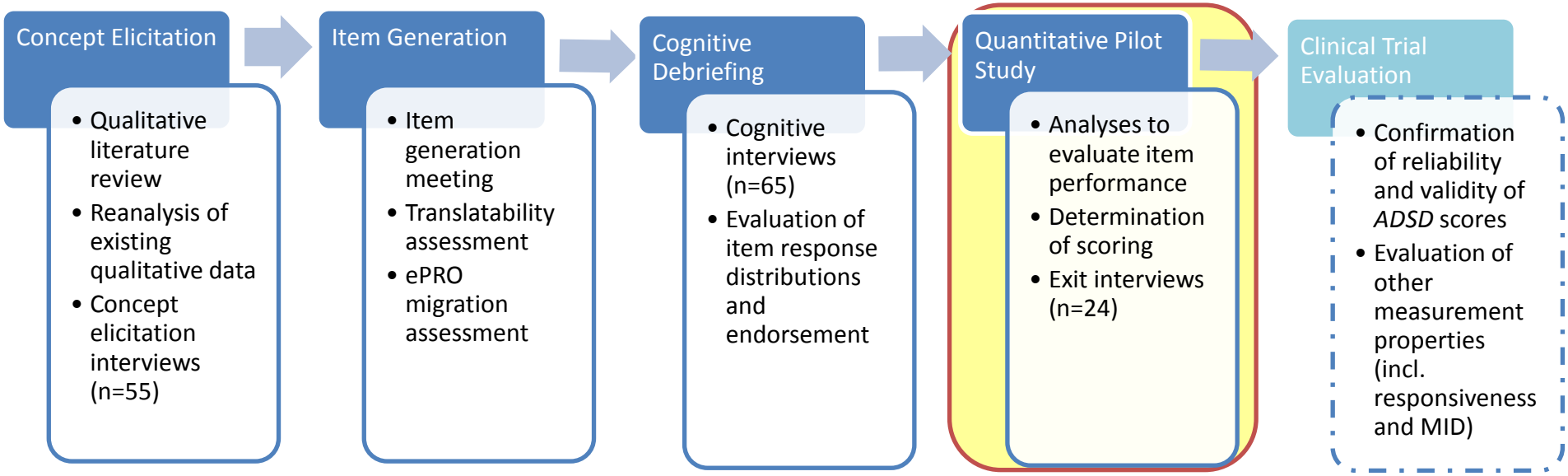
- When asked about the recall period, the FDA stated ***"we agree with the twice-daily reporting frequency and recall periods that you propose."***
- In 209 cognitive debriefing instances, participants were asked about what time period they were thinking of when reading instructions or completing an 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



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



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

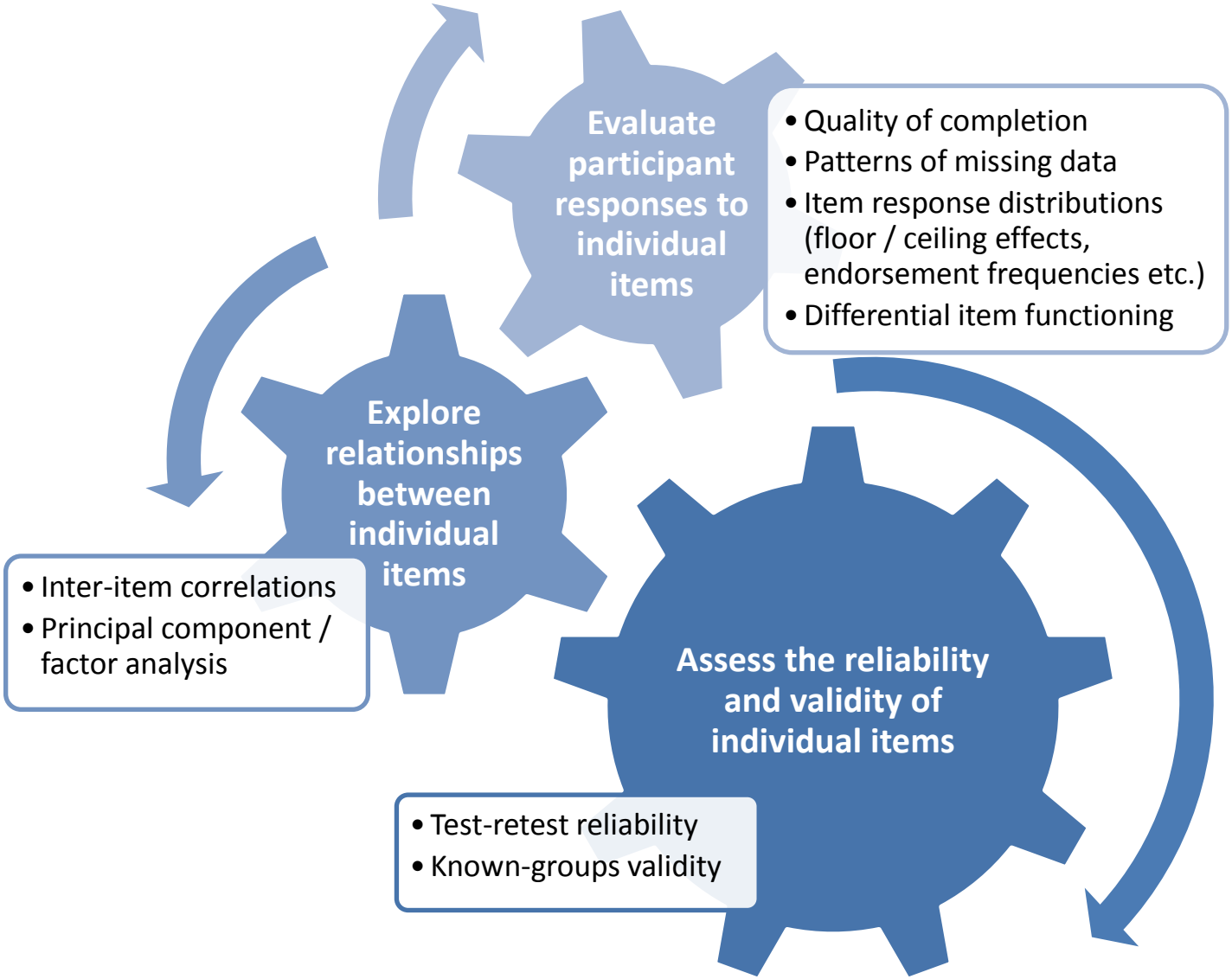
	Schedule of Assessments										
Data Collected	Screening	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Case Report Form (Clinician)	X										
Recruitment Screener (Recruitment agency)	X										
Patient-Reported Data											
Asthma Control Test (ACT)	X										
Asthma Daily Symptom Diary (ADSD)		X	X	X	X	X	X	X	X	X	X
Patient Global Impression of Symptom Severity (PGI-S)		X	X	X	X	X	X	X	X	X	X
Patient Global Impression of Change (PGI-C)											X
Adult Asthma Symptom Diary Scales (AASDS)				X							X

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



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

FDA Feedback to Asthma WG

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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?

Session Participants

Moderator

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

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- Adam Gater, Director, Endpoint Development and Outcomes Assessment, Adelphi Values
- Elektra Papadopoulos, Acting Associate Director, Study Endpoints and Labeling Development, FDA