

# ***Clinical Outcome Assessments in Pediatric Trials: Measurement Gaps, Challenges, and Potential Solutions***

***Eighth Annual  
Patient-Reported Outcome Consortium Workshop***

**April 26 – 27, 2017 ■ Bethesda, MD**



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# Session Participants



## Moderator

- *Sonya Eremenco, MA* – Associate Director, Patient-Reported Outcome Consortium, C-Path

## Presenters

- *Mira Patel, MS* – Graduate Research Associate, Patient-Reported Outcome Consortium, C-Path
- *Sonya Eremenco, MA* – Associate Director, Patient-Reported Outcome Consortium, C-Path
- *Linda Nelsen, MHS* – Senior Director and Head, Patient Centered Outcomes, GlaxoSmithKline
- *Tonya Winders* – President and CEO, Allergy & Asthma Network

## Panelists

- *Linda Abetz-Webb* – Senior Research Director, CEO, Patient-Centred Outcome Assessments
- *Susan McCune, MD* – Director, Office of Pediatric Therapeutics, FDA

# Session Outline



- Clinical trial landscape: Where is the need for pediatric assessment?
- Pediatric measurement tools from ePROVIDE™ review: Do we have the necessary tools to meet the trial measurement need?
- Pediatric Asthma Working Group: Challenges in symptom diaries across a diverse age range
- Parent's Experience and Patient Advocacy Perspective
- Panel Discussion and Q & A

# Introduction

Sonya Eremenco, Associate Director, Patient-Reported Outcome Consortium,  
Critical Path Institute

There is an increased need to assess pediatric populations in clinical trials

- Regulatory requirements
  - US: July 2012 FDASIA permanently reauthorized Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA)
    - PREA: Mandatory pediatric studies: FDA requires assessment of safety and effectiveness of certain products in pediatric patients
    - BPCA: Provides a financial incentive to voluntarily conduct pediatric studies (pediatric exclusivity additional 6 months)
    - For further information:  
<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM452231.pdf>
  - EU (January 2007): Pediatric Regulation enacted
- Scientific rationale
  - “both the safety and efficacy profiles of medications may be significantly different for children than adults due to differences in developmental physiology, disease pathophysiology, or developmental pharmacokinetics and pharmacodynamics”
    - Klassen TP, Hartling L, Craig JC, Offringa M (2008) Children Are Not Just Small Adults: The Urgent Need for High-Quality Trial Evidence in Children. PLoS Med 5(8): e172. doi:10.1371/journal.pmed.0050172

- Challenges
  - Variation in ability of pediatric patients under the age of 12 years to report for themselves due to cognitive and educational development
    - Ability to comprehend symptoms being assessed
    - Ability to read
    - Ability to recall accurately
  - Problems of proxy reporting
    - Literature has shown moderate to poor correlations between self and proxy reports
    - Better correlations with observable phenomena such as behavior and function vs. emotions
  - Limitations of observation and observer reporting
    - Not all relevant symptoms are observable
    - Observer may not be with the child during the day (school/work) or sleeping at night when symptoms occur
    - Discrepancies between self and observer report may occur, who is right?

# Session Objectives



- Review of [ClinicalTrials.gov](https://clinicaltrials.gov) to characterize the clinical trial need in pediatrics with respect to indication, ages, and other study characteristics
- Review of ePROVIDE™ to characterize existing clinical outcome assessment (COA) measures used in pediatric populations with respect to age ranges, disease areas, and measure characteristics
- To describe the Pediatric Asthma Working Group's experience developing a novel COA measurement approach as a solution to challenges in pediatric asthma outcome measurement
- To hear a parent's experience of a child participating in a respiratory trial and more general experiences from a patient advocate regarding a parent's role in the assessment of treatment benefit in pediatric clinical trials



# A Review of Pediatric Trials: Results from ClinicalTrials.gov

Mira Patel, Graduate Research Associate, Patient-Reported Outcome Consortium, Critical Path Institute

- The aim of this review was to use ClinicalTrials.gov to:
  - Identify existing clinical trials in pediatric populations
  - Characterize the scope of the clinical trials with respect to:
    - Indications
    - Age groups
    - Rare disease status

# Description of ClinicalTrials.gov



- ClinicalTrials.gov is a Web-based resource, maintained by National Library of Medicine and National Institutes of Health that provides information on on publicly and privately supported clinical studies on a wide range of diseases and conditions.
- ClinicalTrials.gov was created as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA) which required the establishment of a registry of clinical trials information for both federally and privately funded trials conducted under investigational new drug applications to test the effectiveness of experimental drugs for serious or life-threatening diseases or conditions.
- Information on ClinicalTrials.gov is provided and updated by the sponsor or principal investigator of the clinical study.
- ClinicalTrials.gov became available in February 2000 and the rate of study registration has increased over time.
- Information reported
  - Disease or condition
  - Intervention (for example, the medical product, behavior, or procedure being studied)
  - Title, description, and design of the study
  - Study population: demographic characteristics
  - Requirements for participation (eligibility criteria)
  - [Outcome]
  - [Results]

# Exploration of Pediatric Clinical Trials

## *Methodology*



- Identified clinical trials relevant to PRO Consortium as supporting an indication for labeling through US FDA and registered in ClinicalTrials.gov as of 30-Jan-2017
  - Funding by industry
  - Evaluating a medical intervention in Phase 2 or 3
  - Enrolling children ages 0-17 years of age
- Excluded trials with
  - Interventions not relevant to US FDA CDER/CBER review
  - Populations not relevant to pediatrics
- Age: recoded into lowest and highest per description, and created age groups
  - Infant (<1 year)
  - Preschool (1 to 4 years)
  - Child (5 to 11 years)
  - Adolescent (12 to 17 years)
  - Adult ( $\geq 18$  years)
- Conditions recoded into organ system groupings
  - Flagged rare diseases (Google search of condition)

# Exploration of Pediatric Clinical Trials

## *Search Strategy*

### Inclusion Criteria

- Funder = Industry
- Study Type = Intervention
- Phase = 2 or 3
- Children 0-17
- Search = 30Jan2017

~6000 Trials

### Exclusions for Intervention

- Vaccine (n=823)
- Devices (n=170)
- Procedure (n=108)
- Radiation (n=19)
- Genetic (n=22)
- Dietary (n=56)
- Behavioral (n=35)
- Other (n=14)

### Exclusions for Indications

- Adult Cancer (e.g. breast; prostate) (n=66)
- Dementias of old age (n=17)
- Obstetrics and Gynecology (n=19)
- Newborn (n=52)
- Surgery / Trauma (n=28)

4524 Trials

# Therapeutic Areas/Indications

## *Organ System and Rare Disease Status*



Organ System	Total	% of Total	Rare	% of Group
	(n)		(n)	
Respiratory	723	15.70%	151	20.90%
CNS (Mental Health, Neurology, Behavioral)	625	13.82%	27	4.30%
Infectious	544	12.02%	0	0.00%
Oncology	462	10.21%	0	0.00%
Metabolic	384	8.49%	206	53.60%
Hematology	314	6.94%	35	11.10%
Dermatology	288	6.37%	10	3.50%
GI/Liver	215	4.75%	9	4.20%
Musculoskeletal	198	4.38%	137	69.20%
HIV	175	3.87%	0	0.00%
Cardiovascular	148	3.27%	0	0.00%
Immuno-inflammation	139	3.07%	14	10.10%
Ophthalmology	120	2.65%	10	8.30%
Urinary	87	1.92%	7	8.00%
Endocrine	57	1.26%	25	43.90%
Pain	45	0.99%	0	0.00%
	4524			

# Therapeutic Areas/Indications

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# Understanding Age Ranges

## *Multiple and Overlapping Ages*



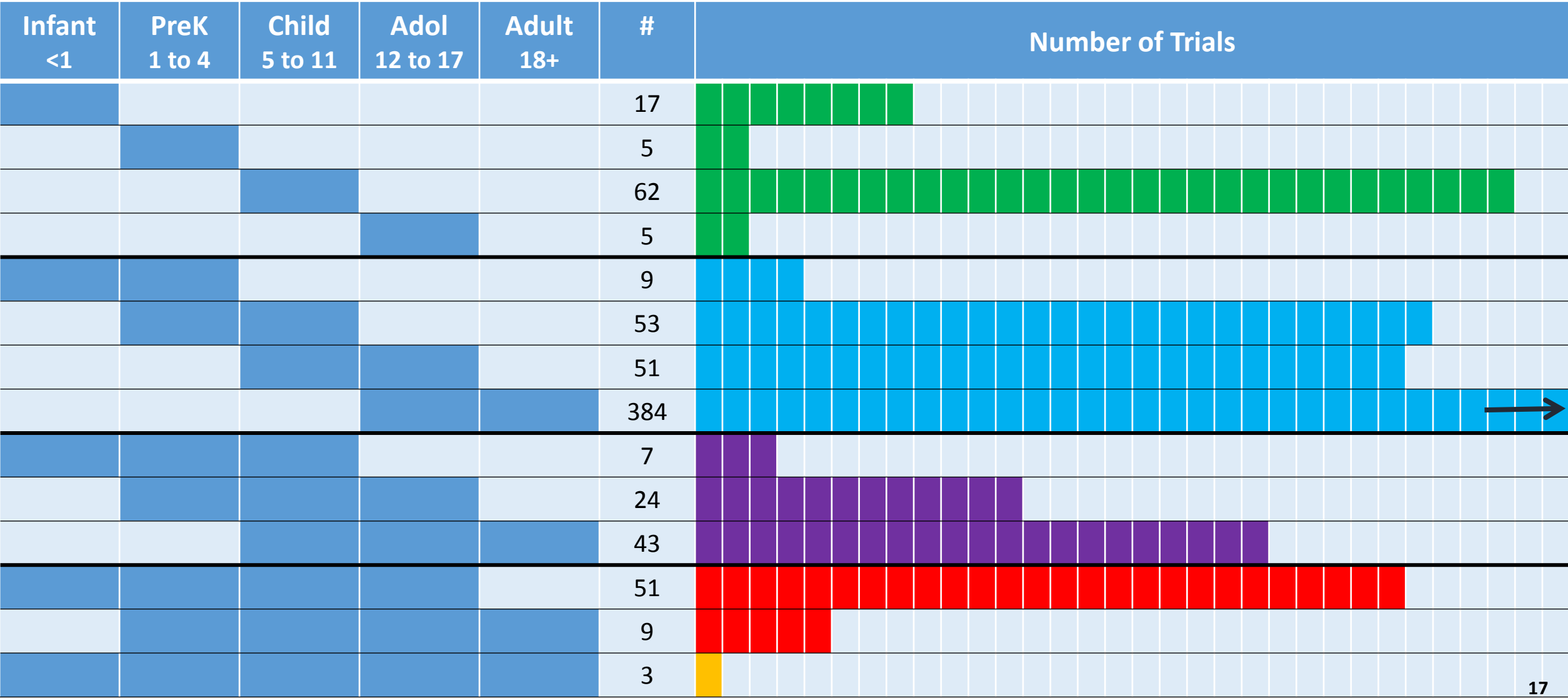
- Inclusion criteria around age were variable
- Age ranges were wide, resulting in challenges for appropriate COAs and consistent endpoints in clinical trials

12 Years and older (Child, Adult)	481
Child, Adult, Senior	410
16 Years and older (Child, Adult)	263
13 Years and older (Child, Adult)	119
6 Years to 17 Years (Child)	109
2 Years and older (Child, Adult)	97
6 Years and older (Child, Adult)	84
12 Years to 17 Years (Child)	82
12 Years to 65 Years (Child, Adult)	74
15 Years and older (Child, Adult)	65
12 Years to 75 Years (Child, Adult)	62
2 Years to 17 Years (Child)	61
6 Years to 12 Years (Child)	52
10 Years to 17 Years (Child)	50
10 Years and older (Child, Adult)	49
up to 17 Years (Child)	43
1 Year and older (Child, Adult)	41
5 Years and older (Child, Adult)	39
6 Years to 11 Years (Child)	39
2 Years to 18 Years (Child, Adolescent)	38



# Respiratory Clinical Trials

## *Multiple and Overlapping Ages*



# Conclusions



- Pediatric clinical trials currently conducted across a wide range of therapeutic areas
  - Respiratory and CNS are most active therapeutic areas
- Age ranges are not standardized and trials encompass widely varying age groups
  - Challenges in development and use of PRO measures that are adequate for wide age ranges
- Rare diseases represent a substantial proportion of pediatric clinical trials for metabolic, endocrine and musculoskeletal conditions and may have implications for PRO measurement needs
- ClinicalTrials.gov represents a valuable source of data to understand trial characteristics to support future COA planning
  - Further exploration of specific diseases and outcomes should be undertaken

# A Review of COA Measures: Results from ePROVIDE™

Sonya Eremenco, Associate Director, Patient-Reported Outcome Consortium,  
Critical Path Institute

The aim of this review was to use ePROVIDE™ to...

- Identify existing COA measures used in pediatric populations; and
- Characterize the scope of the COA measures with respect to:
  - Age ranges
  - Therapeutic areas
  - Type of COA measure
  - Number of items
  - Recall period
  - Response scale
  - Mode of administration
  - Data collection approaches
  - Development year
  - Developer type
  - Origin of measure

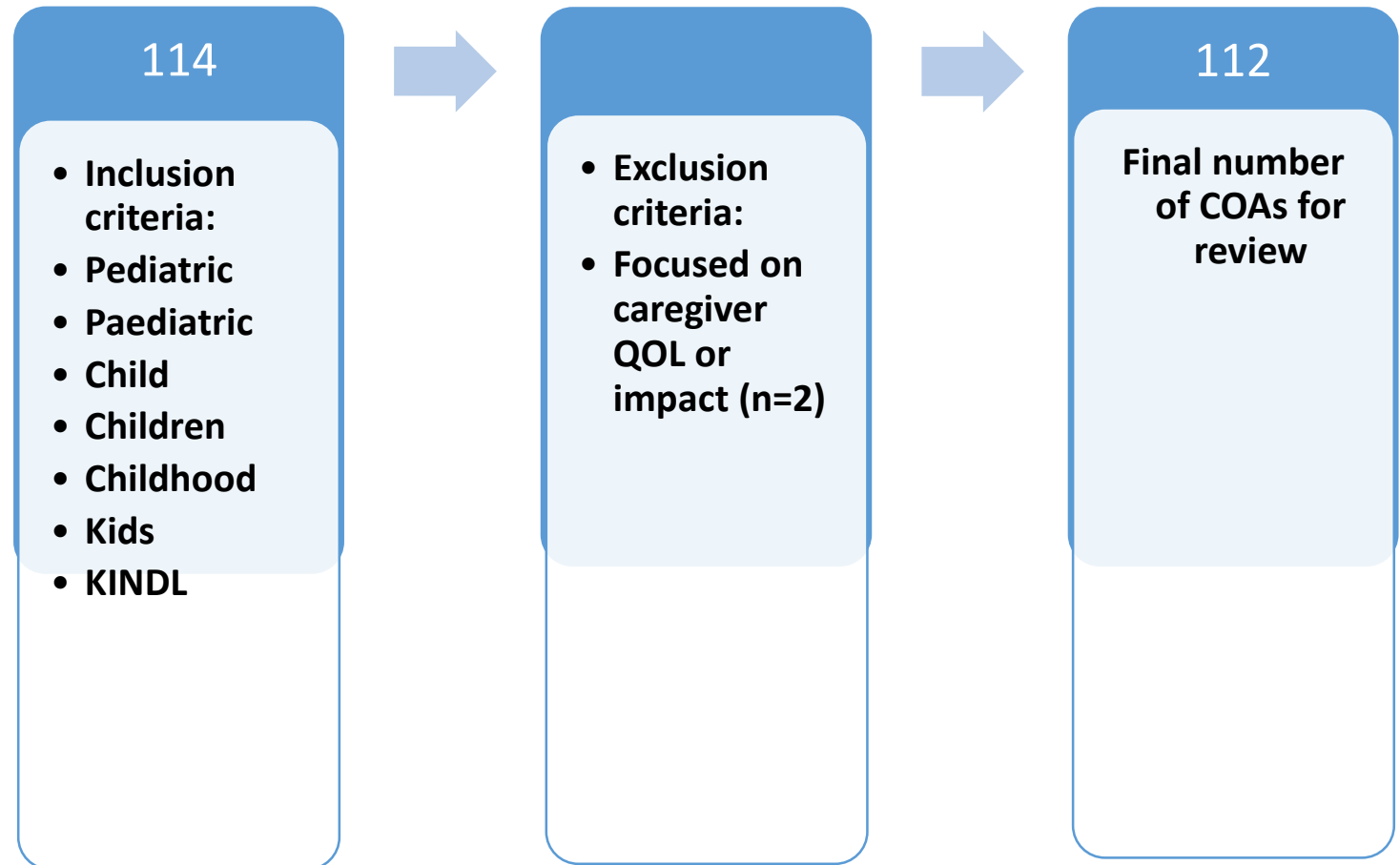
# Description of ePROVIDE™



- In March 2016 Mapi Research Trust launched an e-Commerce platform named ePROVIDE™ which centralizes all its databases, COA request management, and COA instrument distribution:  
<https://eprovide.mapi-trust.org/>
- One unique access for all database content (PROQOLID™, PROLABELS™ and PROINSIGHT™), including a cross-database search engine, allowing searches per type of content, if needed
- PROQOLID™ Database was created in 2002 by Mapi Research Trust to provide a tool for better knowledge and relevant use of COAs and furthermore, to extend access to Patient Centered Outcomes resources for the scientific community
- 1,358 COA measures included

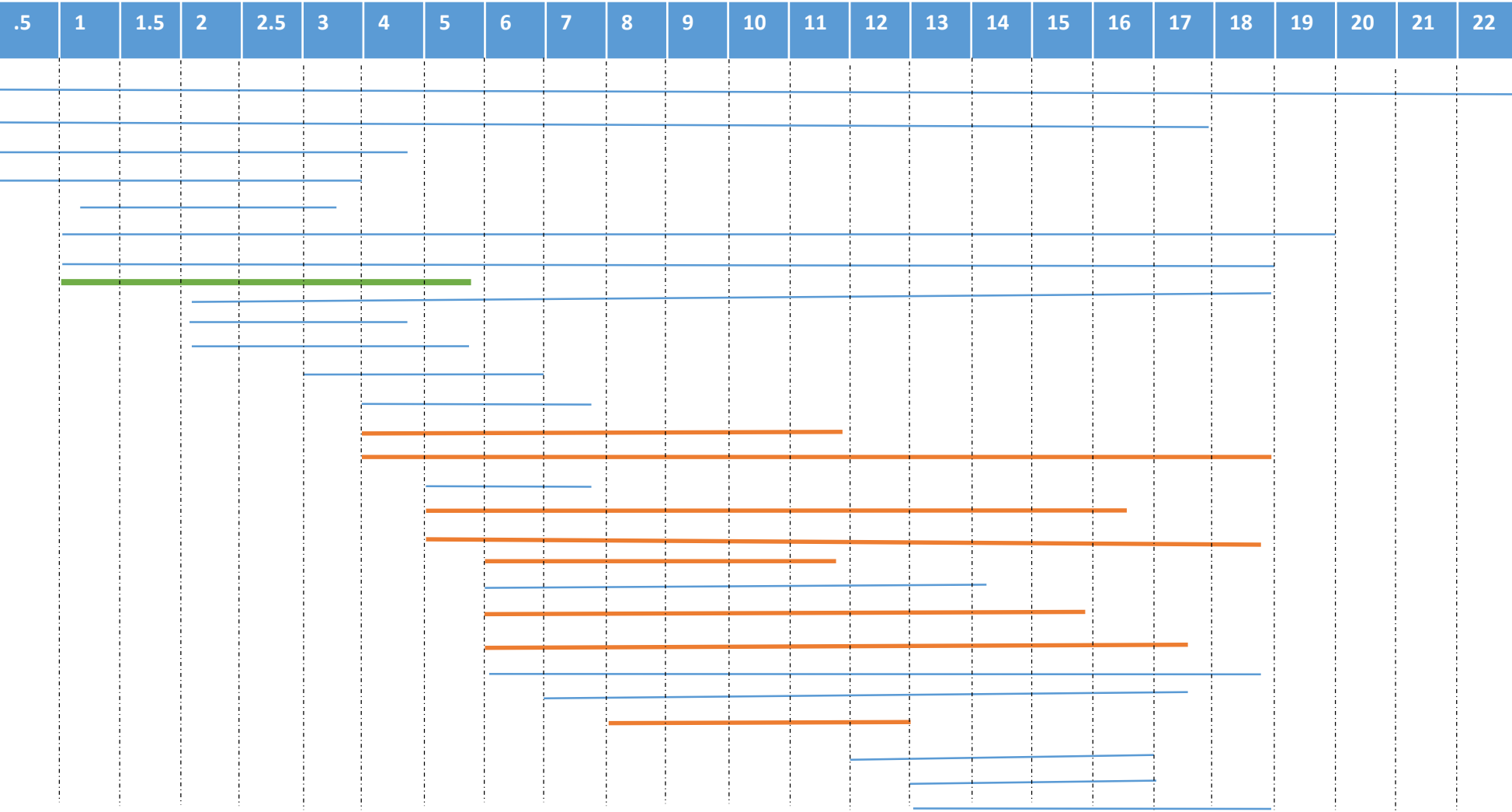
# Search Strategy

- Database: ePROVIDE™
- Search terms
- Measure “Families”
  - 48 “families”
    - 4 with child versions only
    - 44 parent/child versions
  - 2 to 52 measures reviewed per “family”
    - PedsQL includes 26 conditions with parent/child versions of each



- Obtained listed of measure names and acronyms from ePROVIDE™
  - Partial information about the measures from ePROVIDE™
- Retrieved references on measures to obtain more information
- Retrieved measures themselves when possible to obtain more information
  
- Limitations
  - Title search (if term not in the title, measure was not found)
  - Some measures may be missing from the list
  - Partial information depending on what was available in the references

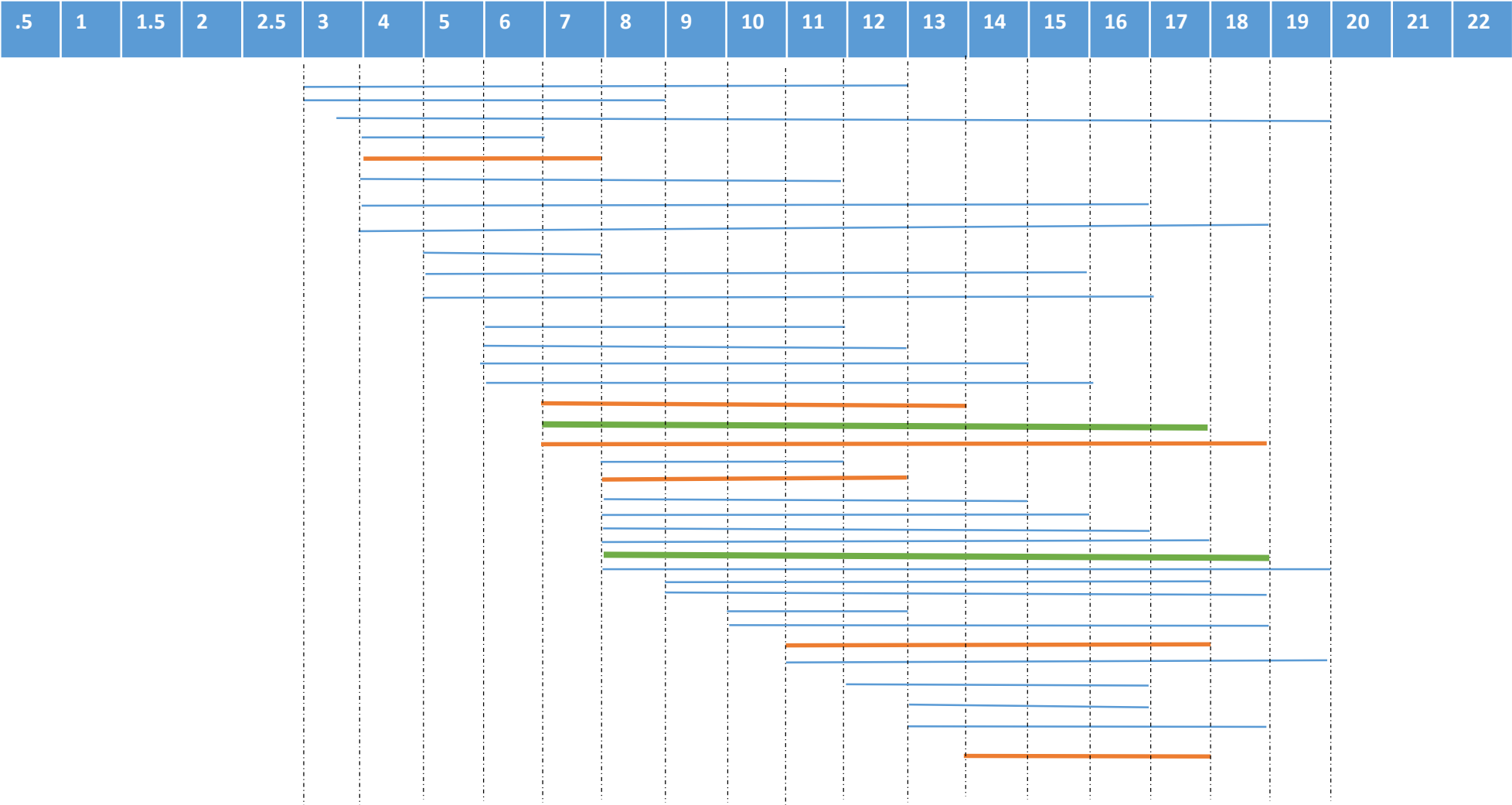
# Results: Parent-report Age Ranges (n=39)



Blue=1 measure    Orange= 2 measures    Green =3 measures



# Results: Child-report Age Ranges (n=46)



Blue=1 measure    Orange= 2 measures    Green =3 measures

# Therapeutic Areas



## ClinicalTrials.gov Categories

- Cardiovascular (n=1)
- Dermatologic (n=1)
- Endocrine: Diabetes (n=3), Obesity (n=1)
- Gastrointestinal/Hepatic (n=5)
- Hematology: Hemophilia (n=2), Sickle Cell Disease (n=1)
- Infectious/HIV (n=1)
- Inflammatory/Autoimmune: RA (n=2)
- Metabolic: Rare disease: Pompe disease (n=1)
- Mental Health/Behavioral (n=10)
- Musculoskeletal (n=1)
- Neurology (n=10)
- Oncology (n=5)
- Ophthalmology (n=1)
- Pain (n=4)
- Respiratory/Allergies (n=10)
- Urinary (n=1)

## New Categories

- Generic (n=18)
- Oral health (n=4)
- Disability (n=1)
- Fatigue (n=1)
- Stem cell transplant (n=1)
- Transplant (n=1)

# Results – Other measure characteristics



- Type of COA:
  - PRO measure=70
  - Proxy measure=44 (majority of so-called ObsRO measures were proxy, not true observer)
  - ObsRO measure=10
  - Parent – unable to distinguish proxy or ObsRO measure=3
  - Composite measure=2
- Number of items: ranged from less than 10 to over 100 across reporter types
  - Child measures = 40% - 20 to 29 items, 20% - 30 to 49 items
  - Parent measures = 27% - 20 to 29 items, 27% - 30 to 49 items
- Recall period: ranged from ‘now’ to ‘past 12 months’
  - ‘past week’ and ‘past 4 weeks’ most frequent for both child and parent reports
  - Next most frequent: ‘None’ for both child and parent reports

# Results – Other measure characteristics



- Response scale: ranged from 2 to 7 levels and visual analog scale (VAS)
  - 3, 4, and 5 level verbal rating scales most common
    - Frequency attribute most common for 3 and 5 levels; intensity for 4 level
  - Faces combined with verbal text (n=34), only 2 cases of faces alone
  - VAS: 4 cases, 2 alone and 2 with faces and text
  - No examples of numeric rating scale (NRS) (common scale for adult measures)
- Mode of administration:
  - Child: 57% self-administered; 38% interviewer-administered; 5% both options
  - Parent: 91% self-administered
  - Composite: Interviewer-administered or both
- Data collection approaches:
  - Paper-based: 96% of child measures and 98% of parent

# Results – Other measure characteristics



- Development year:
  - 85% developed before final FDA guidance for industry on use of PRO measures to support labeling claims was issued (2009), may not meet its recommendations
    - US Food and Drug Administration. *Guidance for Industry – Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. 2009.
- Developer type:
  - Majority developed by universities (56%) or hospitals (20%)
- Origin of measure: 27 adapted from an existing measure
  - 44% adapted from adult measure

# Respiratory Measures - Asthma



Measure	COA Type	Age Range	Recall	Items	Rating Scale	Scale attribute	Mode	Years	Measure type
PedsQL-Asthma, Asthma (short form)	PRO, Proxy	5-7, 8-12, 13-18; 2-4 proxy	1 month, 7 days	28 22	3-pt VRS + faces (5-7) 5-pt VRS (8-18, proxy)	Frequency	Interview (5-7), Self (8-18)	2004 2005	Multi-dimensional HRQOL
PAQLQ Mini-PAQLQ	PRO	7-17	Past week	23 13	7-pt VRS	Bother	Interview Mini: Self for 11 and older	1997 1999	Multi-dimensional HRQOL
Pediatric Asthma Caregiver Diary	ObsRO	2-5	Since woke up, since went to bed	10	Daytime: 6-pt VRS Nighttime: 5-pt VRS	D: severity, interference N: frequency	Self	2000	Symptoms and interference
KINDL® Asthma	PRO, Proxy	7-13, 14-17, 7-17 proxy	Past week	16	5-pt VRS	Frequency, Severity, Intensity	Self	Un- clear	Multi-dimensional HRQOL
C-ACT	Composite	4-11	Child: today/none Parent: last 4 weeks	4 by child, 3 by parent	4-pt VRS + faces (child) 6-pt VRS (parent)	Quality, Problem, Frequency, # of days	Self (parent can help read)	2007	Symptom control
CAQs	PRO	4-7, 8-11, 12-16	Unclear	14, 23, 41	4-pt faces (4-7), 5-pt faces (8-11), 5-pt VRS + faces (12-16)	Happy, B/C: frequency	Self (parent can help read)	1993	Multi-dimensional HRQOL

# Conclusions



- Lack of consensus around optimal age range for child self-report (lowest age 3 to 8) or parent report
  - Interviewer administration essential to facilitate self-report below age 8
- Gaps between therapeutic areas in trials vs. measures available
  - Only one rare disease measure found, few in other therapeutic areas
- Developed for use in clinical practice or epidemiological/population-based research but not clinical trials
- Most developed prior to final PRO guidance (2009)
  - Use of long recall periods (7 days or more), long questionnaires (over 20 items), and parent proxy measures rather than true ObsRO measures
  - Sub-optimal development for clinical trial use to support label claims
- More appropriate and targeted measures are needed to assess treatment benefit from the child and caregiver perspectives in pediatric clinical trials

# **Pediatric Asthma Working Group: *Challenges in symptom diaries across a diverse age range***

Linda Nelsen, Senior Director and Head, Patient Reported Outcomes, GlaxoSmithKline



# Background on Pediatric Asthma WG



- Pediatric asthma has been identified as an area in need of adequate COA tools
  - Current lack of PRO-based labeling claims for pediatric asthma treatment benefit
- *Asthma Daily Symptom Diary (ADSD)* developed for assessment of asthma symptom severity in adolescents and adults (12 years and older)
  - FDA requested that the Asthma WG consider developing COA tools to cover a broader range of asthma patients (i.e., < 12 years old)
- Merck, Asthma WG sponsor, contributed draft versions of an observer asthma diary (OAD) and a child asthma diary (CAD)
  - Diaries developed through content validity but no quantitative evidence
- The Pediatric Asthma WG reviewed the PRO Dossier for OAD and CAD submitted to FDA by Merck noting areas requiring further evaluation and development prior to entering formal qualification process

# Observer- and Child-Reported Diaries



## **Observer diary: completed by parent to record observable signs for children (4 to 11 years)**

- Provides a consistent measure across the age range
- Limited to signs that a parent (observer) can truly observe in the child
  - Unable to report experience of all key symptoms of asthma
  - Created lack of consistency between ADSD and OAD

## **Child diary: self-completed by children 8 to 11 years**

- Supportive measure but not the main endpoint measure
  - Only measure of all key asthma symptoms as identified in ADSD and during pediatric concept elicitation
  - Eliminates direct report of symptoms for children <7 years
- Child completes the diary independent of the parent, so the parent may not know how the child responded

# ADSD and Pediatric OAD/CAD

## *Symptom Concepts and Reporter*



Symptom		ADSD	OAD	CAD
Breathing Symptoms	Difficulty Breathing	+	+	+
	Wheezing	+	+	+
	Shortness of Breath	+	--	+
Chest Symptoms	Chest tightness	+	--	+
	Chest Pain	+	--	--
Cough Symptoms	Cough	+	+	+
	Mucus or Phlegm in Chest	+	--	--

# ADSD and Pediatric OAD/CAD

## *Other Measurement Concepts and Reporter*



Concept	ADSD	OAD	CAD
Symptoms during sleep	--	+	--
Awakenings with Asthma (#)	+	+	+
Activity Limitation	+	+	+
Overall Symptom Severity	+	+	--

# Areas of Concern in OAD and CAD

## *Following FDA review of PRO Dossier*



### **Additional review of transcripts to understand**

- Validity of “difficulty breathing” as an observable concept
- Confirm the patients’ full experience of chest-related symptoms
- The child’s experience and parent’s reporting of nighttime asthma

### **Other concerns**

- Appropriateness of overall disease impact and severity assessments
- Validity of selected response scales

### **Results of additional transcript review**

- Supported symptoms as defined, overall impact and severity items
- Suggested further research to support response scales as optimally framed as severity or frequency

# Considerations

## *Observer- and Child-Reported Diaries*



**Age range of 4 to 11 is challenging with widely variable cognitive development leading to differing abilities to**

- Report symptoms and understand timeframes
- Read and understand the diary questions

**Initial solution was to develop dual diaries**

- Observer-reported diary for caregivers of children ages 4 to 11
- Child-reported diary for children ages 8 to 11

**Limitations**

- Incomplete observation of daytime symptoms by Observer (caregiver) because the caregiver may not be with the child for substantial portions of the day (school, multiple caregivers)
- Incomplete observation of nighttime awakenings by Observer because not observing child
- Some asthma symptoms not observable; limited range of key symptoms (chest tightness, nighttime symptoms) that can be reported by observer (caregiver)
- Inconsistency in symptoms collected from each perspective
- Challenges in defining primary reporter with multiple caregivers (parents, teachers)

# Recording of Pediatric Asthma Symptoms

## *Proposed Co-Completed Diary*



### **Parent and child complete the diary together**

- Parent to administer diary to the child via interview for younger children and contribute observations during the response selection
- In case of discrepant reports, the most extreme (severity or frequency) response to be selected
- Process of administered completion can be adjusted depending on the child's age and ability to self-report.

### **Benefits**

- Allows for a consistent, completely observed assessment of daytime symptoms and nighttime awakenings and symptoms
- Resolves limitations in use of two diaries with respect to limited opportunities for the parent to observe the child during day (school) and at night (sleeping)
- Supports more consistent symptom coverage with *ADSD*

### **Concerns**

- Parent may over-ride child's symptom reports: requires detailed training guide for parents to standardize the co-completion process across respondents.
- Consistency of level of co-completion over the course of a trial; may add variability over time

# ADSD, Co-Completed and Pediatric OAD/CAD

## *Consistency of Symptom Concepts*



Symptom		ADSD	Co-Completed	OAD	CAD
Breathing Symptoms	Difficulty Breathing	+	+	+	+
	Wheezing	+	+	+	+
	Shortness of Breath	+	+	--	+
Chest Symptoms	Chest tightness	+	+	--	+
	Chest Pain	+	--	--	--
Cough Symptoms	Cough	+	+	+	+
	Mucus or Phlegm in Chest	+	--	--	--



# Alternative Approaches to Co-Completion



Approach	Key Elements
<p>Interviewer-administered child diary</p> <p>Supplemented by observer diary</p>	<ul style="list-style-type: none"> <li>• Child diary is an interviewer-administered measure by parent for ages 4 to 11. Parent records the child’s response, with no adjustment at all.</li> <li>• Observer diary is completed by parent for entire age range and represents main endpoint measure.</li> <li>• Parent instructed to consider child’s diary responses and reports and observations of others; consistent with clinical practice.</li> </ul>
<ul style="list-style-type: none"> <li>• Separate diaries</li> <li>• Ages 4 to 7 (observer)</li> <li>• Ages 8 to 11 (self-complete)</li> </ul>	<ul style="list-style-type: none"> <li>• Observer measure for children aged 4 to 7, observable symptoms only.</li> <li>• Child reported measure for children aged 8 to 11, self-completed by child, similar to OAD</li> <li>• Each measure is used in the endpoint.</li> <li>• Issues with pooling data from both within the same trial; independence of reports, ability of observer to consider child (and other observer) reports.</li> </ul>
<p>Composite measure</p>	<ul style="list-style-type: none"> <li>• Diary with items independently completed by child and items by the observer.</li> <li>• Approach used in Childhood Asthma Control Test (C-ACT).</li> <li>• All responses are totaled together into one score.</li> <li>• Potential to be considered a composite endpoint of observer and child asthma symptoms.</li> </ul>

# Pediatric Symptoms

## *Benefits of Co-Completed Diary Approach*



- Allows for a consistent, completely observed assessment of daytime and nighttime symptoms recognizing limitations inherent in individual reports
- Increases reliability of symptom reports by
  - Supporting reports of young children
  - Supplementing reports by parent not able to observe child for much of a day or night
- Supports a single measurement approach across an age range with varying cognitive and reading abilities
- Innovative approach to the complex problem of gaining insight into pediatric asthma treatment experience

# Parent's Experience and Patient Advocacy Perspective

Tonya Winders, President and CEO, Allergy & Asthma Network

# Parent's Experience



- Jennifer Martin story
- 15 year-old son in two clinical trials over past 5 years
- Works part-time, busy mother of three with her own health issues
- Chris at school and after care
- Challenges: Time, cost, diary recording
- Opportunities: Help others, help child, get meds free
- Frustrations: Learning about trials, participating in trials, not knowing outcome of trials

# Patient Advocacy Perspective



- Less than 1% of patients ever hear about clinical trials
- General lack of awareness of community-based PCP and specialists about opportunities to participate in research
- Parental fear of harming child
- Chronic vs acute vs life-threatening disease
- Parental fear of someone judging them and/or child
- Low health literacy
- Most common concerns voiced:
  - Time
  - Money
  - Inability to monitor and report accurately—school, childcare provider, nighttime, second hand vs first person
  - Letting the doctor down

# Panel Discussion and Q & A



## Moderator

- *Sonya Eremenco, MA* – Associate Director, Patient-Reported Outcome Consortium, C-Path

## Presenters

- *Mira Patel, MS* – Graduate Research Associate, Patient-Reported Outcome Consortium, C-Path
- *Sonya Eremenco, MA* – Associate Director, Patient-Reported Outcome Consortium, C-Path
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- *Susan McCune, MD* – Director, Office of Pediatric Therapeutics, FDA

# Supplemental Slides

# ePROVIDE™ Analysis Tables





# Measure Characteristics – Range of items



Number of items	PRO measure	Proxy measure	ObsRO measure	Parent-report unable to verify	Composite
<10	9	5	1		2
10 to 19	11	5	1	2	
20 to 29	28	12	3		
30 to 49	14	12	3		
50 to 100	7	9		1	
Over 100	1	1	2		
Total (129)	70	44	10	3	2

# Measure Characteristics – Recall period



Recall period	PRO measure	Proxy measure	ObsRO measure	Parent-report unable to verify	Composite
None/in general	4	4	2		1
Now/currently	3	2			
Past 24 hours or less	1		1		
Past week/7 days	30	25	2		1
Past 2 weeks	2		1		
Last few weeks	1	1			
Past 4 weeks/month	31	26		1	1
Past 2 months		1			
Past 3 months	3	2		1	
Past 6 months		1			
Past 12 months	1		1		
Compared to 1 year ago	1	1			
Not reported	10	6	3	1	

# Mode of Administration and Data Collection

Characteristic	PRO measure	Proxy measure	ObsRO measure	Parent-report unable to verify	Composite
Administration					
Self	54	40	6	6	
Interviewer	36		2	1	1
Both mentioned	5	1	1		1
Data collection					
Electronic	4			1	
Paper (assumed)	91	41	9	7	2

# Response Scale – Child Measures

Type of Response Scale	2 levels	3 levels	4 levels	5 levels	6 levels	7 levels	VAS
Verbal rating scale	Yes/no (2)	Varying attributes (1) Frequency (29) Severity (1) Limitations (1)	Intensity (4) Frequency (3) Severity (1) Quality (1) Probability (1) Difficulty (1)	Importance (1) Difficulty (2) Frequency (33) Intensity (3) Severity (3) Interference (1) True (1)		Bother (3) Frequency (1)	
Likert-type			Agreement (1) Good to bad (1)				
Faces/drawings and verbal ratings	Yes/no (1)	Frequency (24)	Label unclear (1) Pain intensity (1) Intensity (1) Circles Good to bad (1) Circles Like to dislike (1)	Frequency (2) Severity (1) Happy to unhappy (1)			
Faces only			1	1			
VAS and faces							Smiley (2)
VAS							Pain (1) Global (1)
Props	Bears (1)						

# Estimated Development Year



Categorized COA measures by the year range in regards to the development of the FDA PRO Guidance:

- <2006 (prior to guidance)
- 2006-2009 (draft guidance issued)
- >2009 (final guidance issued)

Years	Number of COA Measures
Missing	4
<2006	56
2006-2009	17
>2009	10

# Developer Type



- Academic Institution (n=50)
- Hospital (n=18)
- Consulting Organization (n=8)
- Non-profit/government (n=7)
- Industry (n=6)

# Origin of Measure

- Adapted from adult measure (n=12)
- Adapted from parent measure (n=1)
- Adapted from adolescent measure (n=3)
- Adapted from a child measure for younger children (n=2)
- Parent and child versions developed simultaneously (n=6)
- Parent measure adapted from another parent measure (n=3)

# Age Groups

- Frequency counts were conducted to:
  - Determine how many trials fell into each age range
  - Determine how many trials from the “0-17 years” category fell into each pediatric age range

Age Range	Number of Trials
0-17 years	1619
18-69 years	941
70+ years	2243

Pediatric Age Range	Number of Trials
<1 year	1191
1-5 years	2125
6-11 years	2711
12-17 years	4159