

Developing a Pediatric COA Measurement Strategy *A Case Study in Asthma*

***FIFTH ANNUAL
PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP***

April 29 - 30, 2014 ■ Silver Spring, MD

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Session Participants



Moderator

- *Elisabeth Piault-Louis, PharmD, MA* – Senior PRO Scientist, Genentech

Presenters and Panelists

- *Linda Nelsen, MHS* – Director, Patient Reported Outcomes, GlaxoSmithKline
- *Louis Matza, PhD* – Senior Research Scientist, Evidera
- *Elektra Papadopoulos, MD, MPH* – Team Leader, Study Endpoints Team, SEALD, OND, CDER, FDA
- *Rob Arbuckle, MA, MSc* – Director, Endpoint Development & Outcomes Assessment, Adelphi Values
- *Laura Lee Johnson, PhD* – Statistician, National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health (NIH)
- *Andrew E. Mulberg, MD, FAAP, CPI* – Deputy Director, Division Gastroenterology and Inborn Error Products, CDER, OND, FDA
- *Hari Cheryl Sachs, MD* – Pediatric Team Leader, Pediatric and Maternal Health Staff, OND, CDER, FDA

Agenda

Designing Endpoints for Pediatric Development



Topic	Presenter	Time
Introduction	L Nelsen	10
Summary of the ISPOR PRO Good Research Practices for assessment of children and adolescents	L Matza	15
How can we understand a disease as experienced by children?	R Arbuckle A Mulberg	15
How do you select a reporter and what questions do you need to consider?	H Sachs L Matza	15
How do we construct endpoints to support treatment benefit claim across age ranges?	LL Johnson	15
Open panel discussion Wrap up	E Papadopoulous	10

Endpoints and Clinical Outcome Assessments in Pediatric Asthma

Linda Nelsen

Director, Patient Focused Outcomes
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Pediatric Asthma

Examples of Current US Labels



Label Attribute	Asthma Drug 1 (AD1)	Asthma Drug 2 (AD2)
Indication	AD1 is ... indicated for treatment of asthma in patients aged 4 years and older	AD2 is indicated for prophylaxis and chronic treatment of asthma in patients 12 months of age and older
Clinical Studies: Primary Objective	Determine the safety of AD1...study also included secondary efficacy measures of pulmonary function	<ul style="list-style-type: none"> • FEV1 percent change from baseline (6 to 14 years) • Safety and tolerability of AD2 in [2-5 year old] age group
Clinical Studies: Results	...Extrapolation of efficacy data from patients aged 12 years and older, support the conclusion that AD1 is efficacious in the treatment of asthma in patients aged 4 to 11 years	Findings of exploratory efficacy evaluations support the overall conclusion that AD2 is efficacious in the maintenance treatment of asthma in patients 2 to 5 years

July 2010: FDA QRT Response to Scoping Summary Document

- While we acknowledge that symptom measurement in asthma is important, measurement and reporting of these individual symptoms is currently well-defined and standardized. ..
- We recommend you consider developing **separate age-appropriate asthma symptom measures for use with the pediatric population** (age 11 years and younger).
- **Evaluation of asthma symptoms in pediatric patients** or in the context of defining and characterizing asthma exacerbation, remain two **areas of great clinical significance without a uniform regulatory pathway**

November 2010: FDA QRT Response to Asthma WG

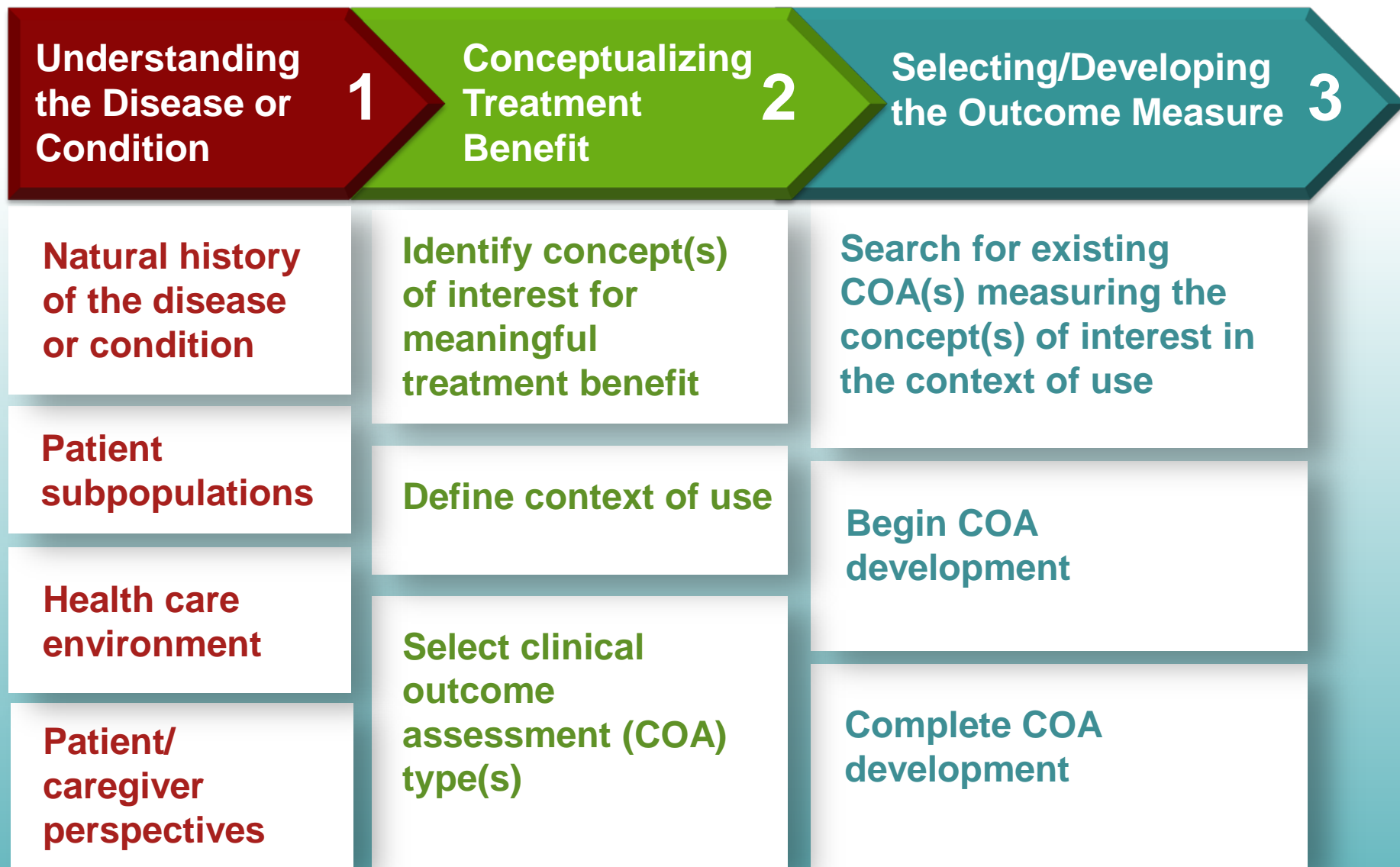
- FDA has re-evaluated your request and now concurs that the development of an adequate measure of the specific symptoms of persistent asthma in adolescents and adults aged 12 years and older would be useful in the support of efficacy claims...
- We also strongly recommend that **you include age-appropriate asthma sign/symptom assessment measures for use in children aged 11 years and younger** in your instrument development program.
- It is **unclear if the same instrument developed for use in the adult population will be appropriate and interpretable for children 12 to 17** years of age.
- It is recommended that a separate qualitative evaluation is performed for children 12 to 17 years of age.

FDA to Asthma WG – September 2012

Following DDT submission of Qualitative Research Protocol:

- This will be a valuable drug development tool in its own right, but we would like to **also encourage you to expand the scope of the asthma patient population to address a public health measurement priority—age appropriate symptom measures for the pediatric population age 11 years and younger.**
- As you are aware, trials for small children will be more feasible using well-designed and reliable scales because spirometry is inappropriate in small children <5-6 years.
- Good instrumentation will also facilitate trial measurement with older children.
- As sponsors move forward with applications needed for the pediatric population, we are hopeful the Asthma Working Group will leverage its expertise to move ahead with pediatric measures.

Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials



Developing Pediatric Patient-Reported Outcome (PRO) Instruments for Clinical Trials to Support Medical Product Labeling: Challenges and Good Practices

Louis Matza
Evidera

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Based on the Work of a Recent ISPOR Task Force



- John J. Alexander, MD; Food & Drug Administration
- Monika Bullinger, MD, PhD; University of Hamburg
- Louis Matza, PhD (Chair); Evidera
- Donald Patrick, PhD, MSPH (Co-Chair); University of Washington
- Andreas Pleil, PhD; Pfizer Global Pharmaceuticals
- Luis Rajmil, MD, MPH, PhD; Catalan Agency for Health Technology Assessment and Research
- Anne Riley, PhD, MS; Johns Hopkins University

Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

- Issues “for pediatric PRO instruments are similar to the issues detailed for adults.”
- However, there are “additional issues” when developing PRO instruments for children and adolescents.
- Several challenges are mentioned, but specific recommendations are not provided.

Task Force Objectives



- Suggest good practices for pediatric PRO research conducted to inform regulatory decision-making and support claims made in medical product labeling.
- Highlight areas where further research on pediatric PROs is needed.
- Current paper differs from previous reviews because of its specific focus on pediatric PRO instruments in the context of medical product development and labeling (i.e., “the regulatory context”)

**Good Practice 1:
Consider Developmental
Differences and Determine Age Cutoffs**

- This is a key issue in choosing and developing measures for children.
- Common Questions:
 - At what age can children begin to report their health status?
 - At what age are children’s responses reliable?
 - At what age can children respond to items assessing more abstract concepts?
 - Can an 11-year-old complete a questionnaire originally developed for children 12 and over?

Age Groupings for Reports by Children: Broad Guidelines



- The answer: “It depends”
- Age groupings are proposed and described
- However, these will not apply to all situations or all children

Four Age Groups

Age Range (in years)	Reliability of Child Self- Report	Comments on PRO Assessment in the Regulatory Context
Under 5	No evidence	<ul style="list-style-type: none">• Must rely on informant-report.
5-7	Marginal	<ul style="list-style-type: none">• More research is needed.• Child-Report appears unlikely to yield results acceptable for regulatory decision-making.
8-11	Varies, but often acceptable	<ul style="list-style-type: none">• Child-report may be acceptable in some cases, depending on the domains being assessed.• Qualitative research will need to clearly show that children understand the PRO instrument as intended.
12-17	Good	<ul style="list-style-type: none">• Self-report is recommended in most cases.• Must demonstrate content validity in the target age group; generally unacceptable to use adult measures.

Determining Age Appropriateness of a PRO



- Age-appropriateness of a PRO should be documented with a combination of qualitative and quantitative research.
 - Qualitative research to examine whether the instrument has the right content and is appropriate for the target age group.
 - Quantitative research to examine psychometric properties in a sample matching the intended age range in planned clinical trials.

Good Practice 2: Establishing Content Validity of Pediatric PROs

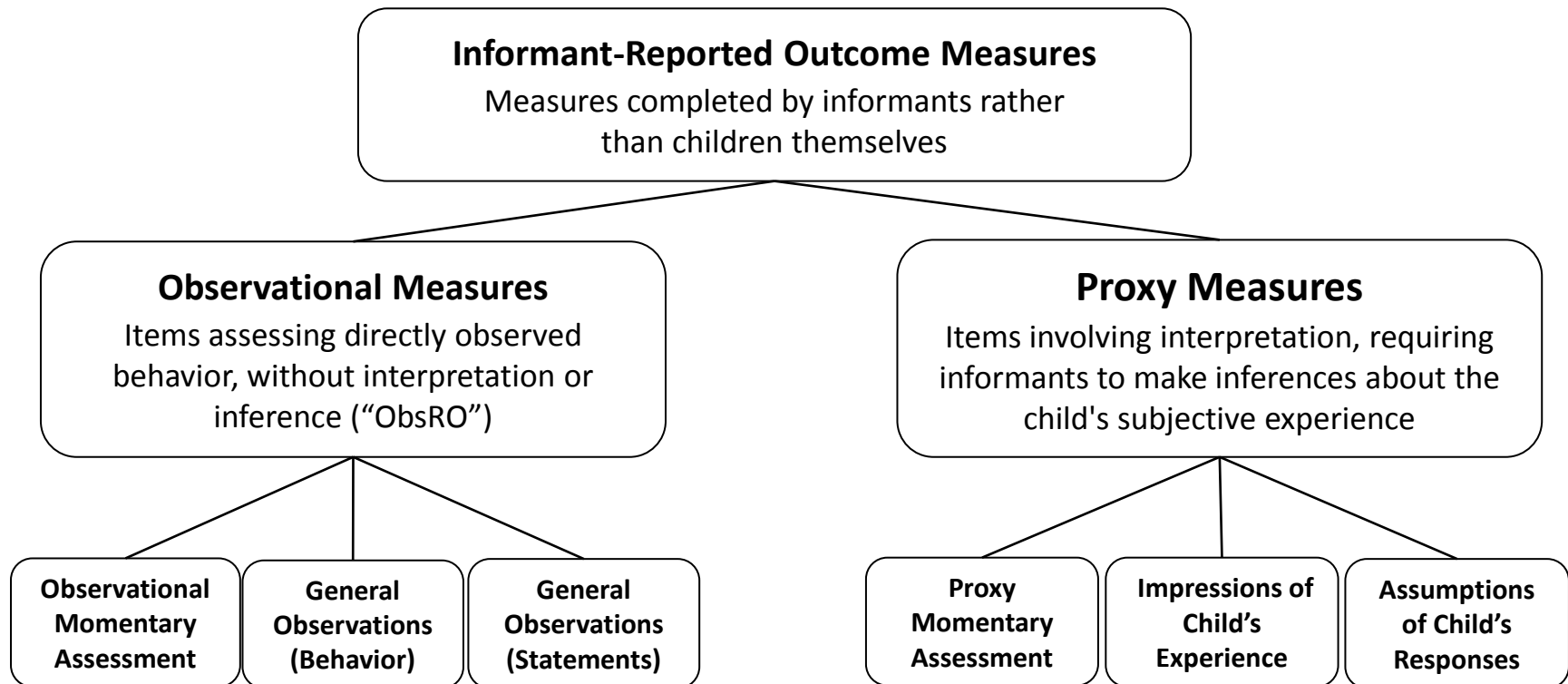
- Definition: The extent to which an instrument contains relevant and important aspects of the concept it intends to measure.
- For the medical product labeling context, evidence is required to demonstrate that the instrument measures the targeted concept.
- Content validity is established via qualitative research with direct input from the target population.
 - Step 1: Concept elicitation
 - Step 2: Cognitive interviews

- Children and adolescents can be effective content experts
- Data may be gathered in interviews or focus groups.
- We recommend interviewing several types of respondents, including the children themselves, parents, and clinicians.

- Respondents complete a proposed set of items
- Then, they are asked about clarity, comprehensibility, comprehensiveness, and relevance of items.
- Developmental appropriateness is a central issue to be considered during the cognitive interview process.
- Respondents should be from the target population. If a child-report measure is being developed, children should be the respondents in the cognitive interviews.

**Good Practice 3:
Determining Whether an Informant-Reported
Outcome Instrument is Necessary**

Types of Informant-Reported Outcome Measures for Pediatric Assessment



- FDA PRO guidance: Informant measures should be observational rather than proxy.
- Parent-report measures are likely to be most accurate and reliable when the items focus on observational content.
- This task force agrees with this recommendation for research conducted for use in the regulatory context.
- Still, proxy-report measures have yielded important information about child health and functioning, and this task force does not want to discourage future research involving parent proxy measures.

1. When children in the target age range are generally capable of reliably reporting the domains of interest, a child-reported measure should be used.
2. When children are not capable, an informant-report measure may be used.
3. When using an informant-report measure, items should assess observable content as much as possible, rather than subjective aspects of the child's experience.

**Good Practice 4:
Ensure that the Instrument is Designed
and Formatted Appropriately
for the Target Age Group**

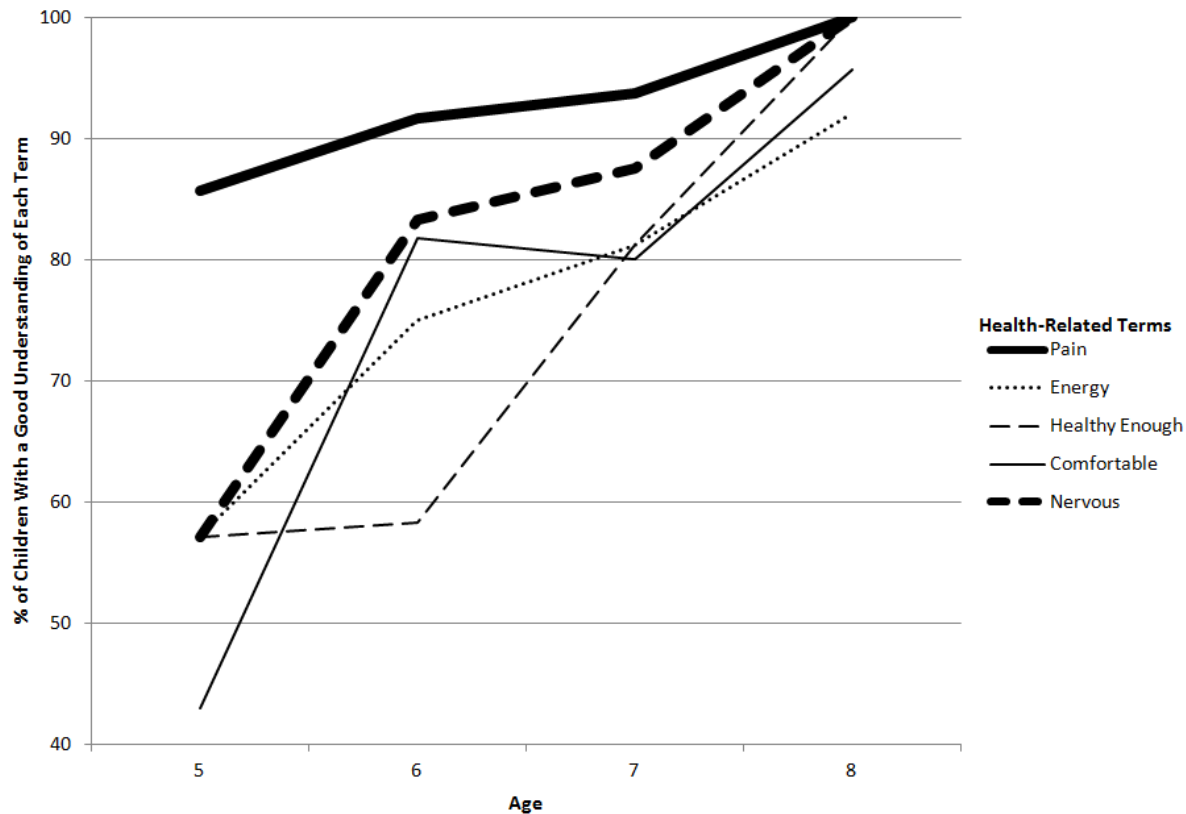
Age-Appropriate Instrument Design and Format



- In the task force manuscript, we discuss aspects of instrument design that must be considered to ensure that a PRO instrument is developmentally appropriate for a target age.
- Recommendations are provided based on developmental trends reported in available published studies.
- We encourage more qualitative research focusing on ways to most effectively format and design PRO measures.

One Example: Health-Related Vocabulary and Reading Level

- Children's health-related vocabulary increases with age.
- Rebok et al. (2001) illustrate this developmental trajectory across four age groups



Other Instrument Design and Formatting Issues to Consider (See Manuscript for Details)



- Response Scale
- Recall Period
- Length of Instrument
- Pictorial Representations (e.g., smiley faces, pictorial representations of individual items, circles of graduated sizes)
- Other Formatting Details (layout of items, large print)
- Administration Approaches (e.g., degree of independence, technology)
- Electronic data collection

Good Practice 5: Consider Cross-Cultural Issues

- Pediatric measures may raise issues different from those in research with adults.
 - Differences in educational systems across countries: reading ability at any given age may vary.
 - Cultural differences in the type of information that is conveyed to children about disease and treatment.
 - Cultural differences in children's willingness to talk to interviewers.
- Future research is needed.

- For each individual study, the optimal PRO approach will depend on a range of factors including the child's age, the medical condition of the target population, and the constructs being assessed.
- The task force report presents general guidance and discusses the issues that must be considered when designing, validating, or implementing pediatric PRO instruments for use in the context of regulatory submissions and medical product labeling.

Conclusions (cont'd)



- Different PRO approaches may be advisable for research that is not intended to support medical product labeling or regulatory decisions.
- There is empirical research supporting many of our recommendations, and these studies are cited throughout the paper. Further research is needed in most areas.

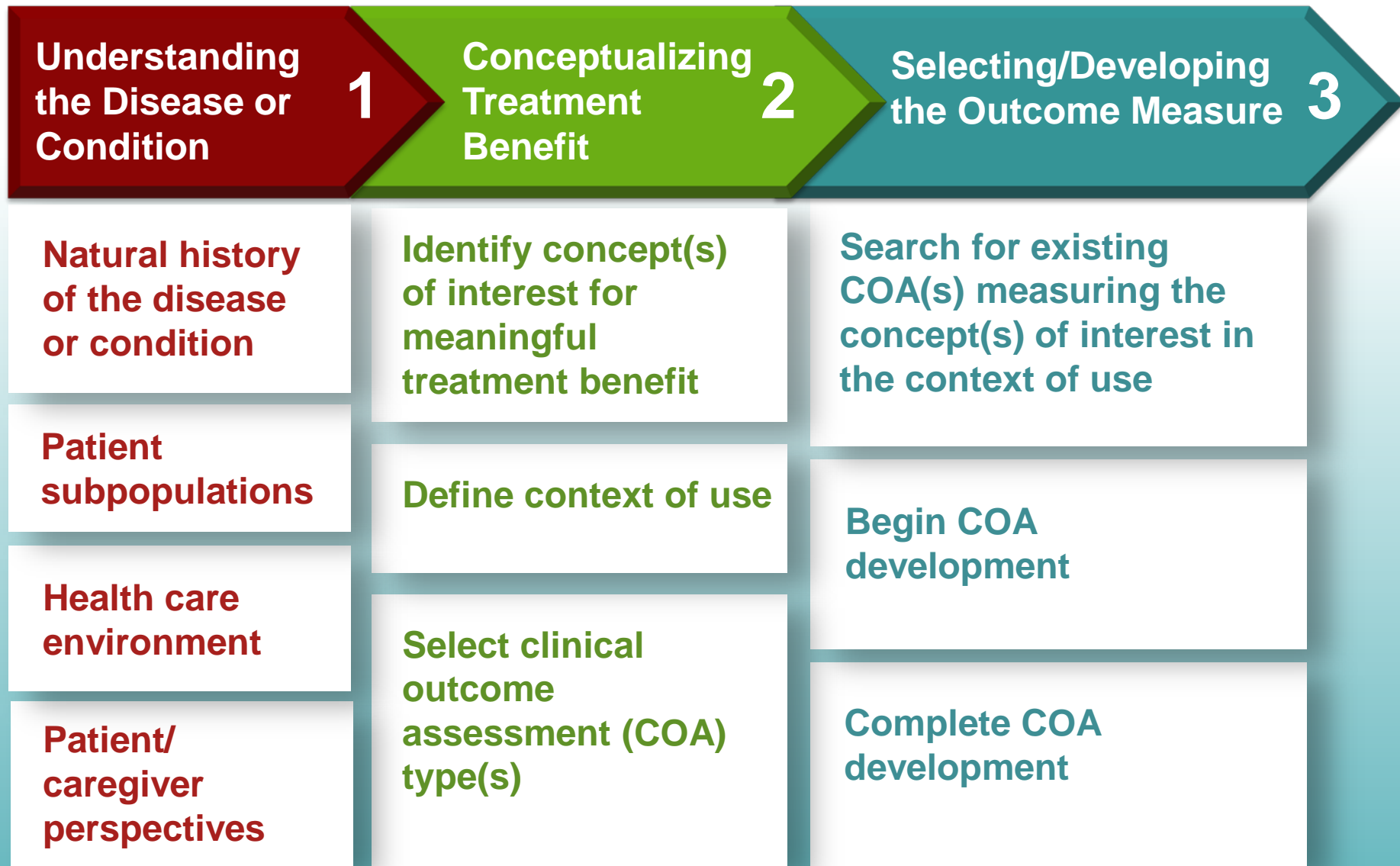
Directions for Future Research



- Provide **updated informant-report instruments**, emphasizing observational (rather than proxy) content.
- Research on optimizing PRO design for **younger children** is needed.
- Studies comparing **multiple measurement approaches** may help provide more specific recommendations than are currently available.
- There are not yet many published studies that have examined content **validity of PROs for children**. More research is needed to examine and refine these methods.
- Interpretation of data from **multiple reporters**: Both parents and children may be able to provide useful information, but results could be difficult to interpret if they have different opinions of the same construct.
- Interpretation of data from **multiple age groups**: Some PRO instruments have different forms for different age groups.

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- **Citation of the task force report:** Matza LS, Patrick DL, Riley AW, et al. Pediatric patient-reported outcome instruments for research to support medical product labeling: report of the ISPOR PRO good research practices for the assessment of children and adolescents task force. *Value Health*. Jun 2013;16(4):461-479.

Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials



Understanding the Disease or Condition

- How can we understand a disease as experienced by children?
 - How does the child experience of symptoms differ from the adults?
 - Is this due to a true difference in symptoms or different perception or articulation of children and adults?
- What are the factors to consider when determining that a population could self-report vs. a population who needs to rely on an informant assessment?

How can we understand a disease as experienced by children?

Rob Arbuckle - Adelphi Values
Andrew Mulberg - FDA

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Disease experience/concept elicitation in children



- Concept elicitation is a critical stage in PRO and ObsRO instrument development
 - Identify and understand the “Concept(s) of Interest” through in-depth qualitative research with the relevant patient population (“Context of Use”)
 - For pediatrics can include interviews with children, caregivers, clinicians and sometimes teachers, physical therapists, etc
- Well conducted, in-depth qualitative research within narrow age ranges is particularly important in pediatrics
 - what words and phrases do children of different ages use and understand
 - what concepts they are familiar with and can they reliably report on

Disease experience/concept elicitation in children



- Many additional challenges associated with concept elicitation in pediatrics
 - Children can be:
 - shy and reticent
 - intimidated by the interview setting
 - easily bored
 - confused by unfamiliar vocabulary
 - Other reporters (e.g. parent/caregivers):
 - cannot report on concepts that are not observable
 - May not observe the child often enough or closely enough
 - May taken into account information provided by others

Experience of the disease/concept elicitation in children



- How does the child symptom experience differ from that of adults?
- How to determine if apparent differences are due to a true difference in symptom experience or a difference in the ability of the child to articulate their experience?
Dependent on:
 - Intellectual ability/developmental stage
 - Vocabulary
 - Confidence/comfort with interview situation or answering a questionnaire
- Some apparent differences may be due to the ability of the child to participate in the interview/complete a measure?
- What techniques can you use to help children to talk about their symptoms during concept elicitation interviews?

- Interviewing language has to be age/ developmentally appropriate, tailored to the specific child
 - Cannot just ‘adapt’ parent interview guide
 - Ask parent what words the child understands for key concepts before the start of the interview
- Avoid leading questions and excessive repetition of question
 - If a question is repeated children can try to give the ‘right’ answer
 - Drawings, creative exercises, tools (e.g. “talking mats”) and toys/props can be used to help the child to relax and to talk

Experience of the disease/concept elicitation in children

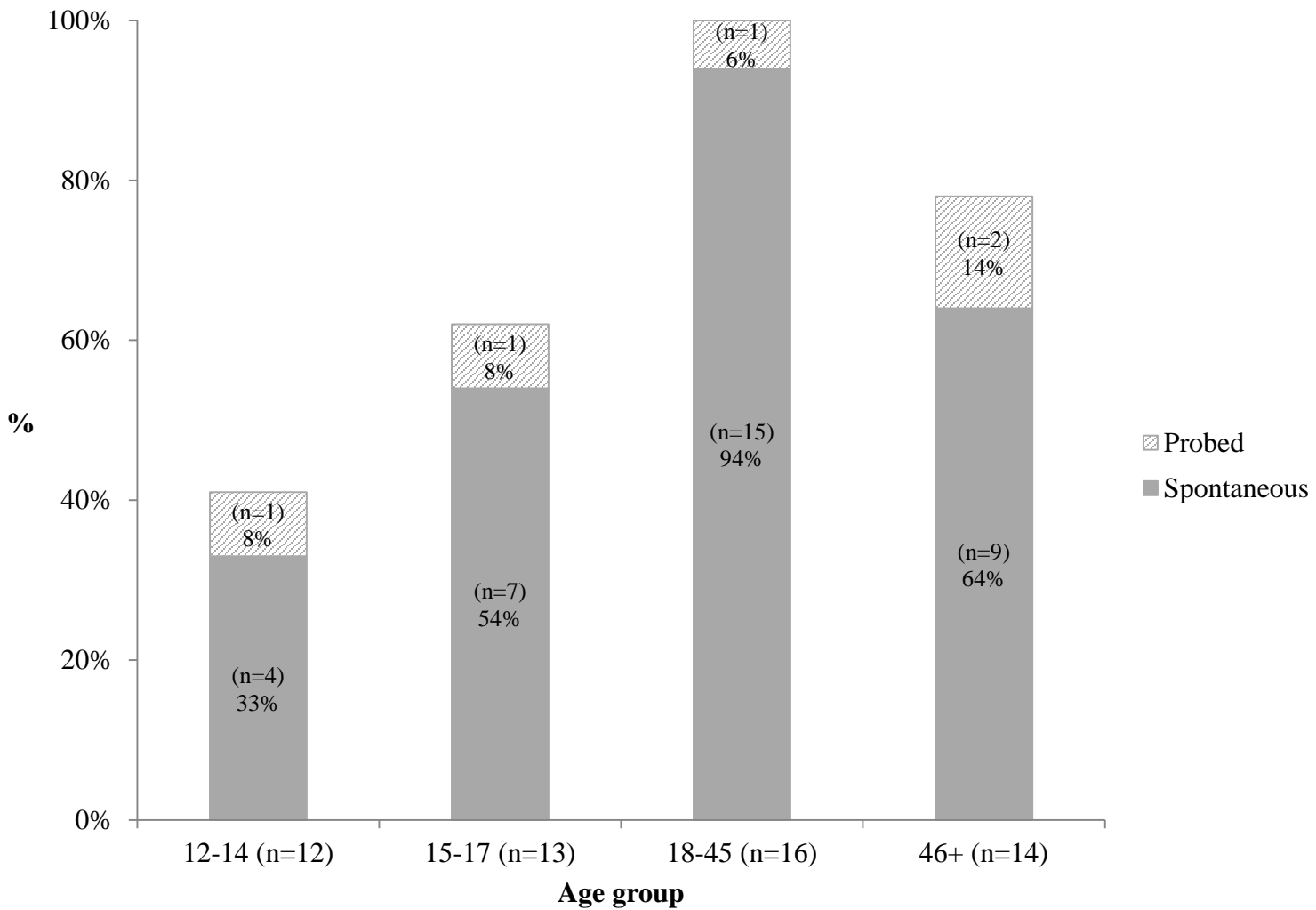


- Children often use terms to refer to symptoms or bodily parts that can be specific to their geographical region, social group, or even family
 - e.g. “boogers” vs “snot” vs “icky stuff”
 - Solution: ask parent for the appropriate word before an interview
 - For actual PROs, is it acceptable for parents to paraphrase PRO questions to help the child understand the meaning?

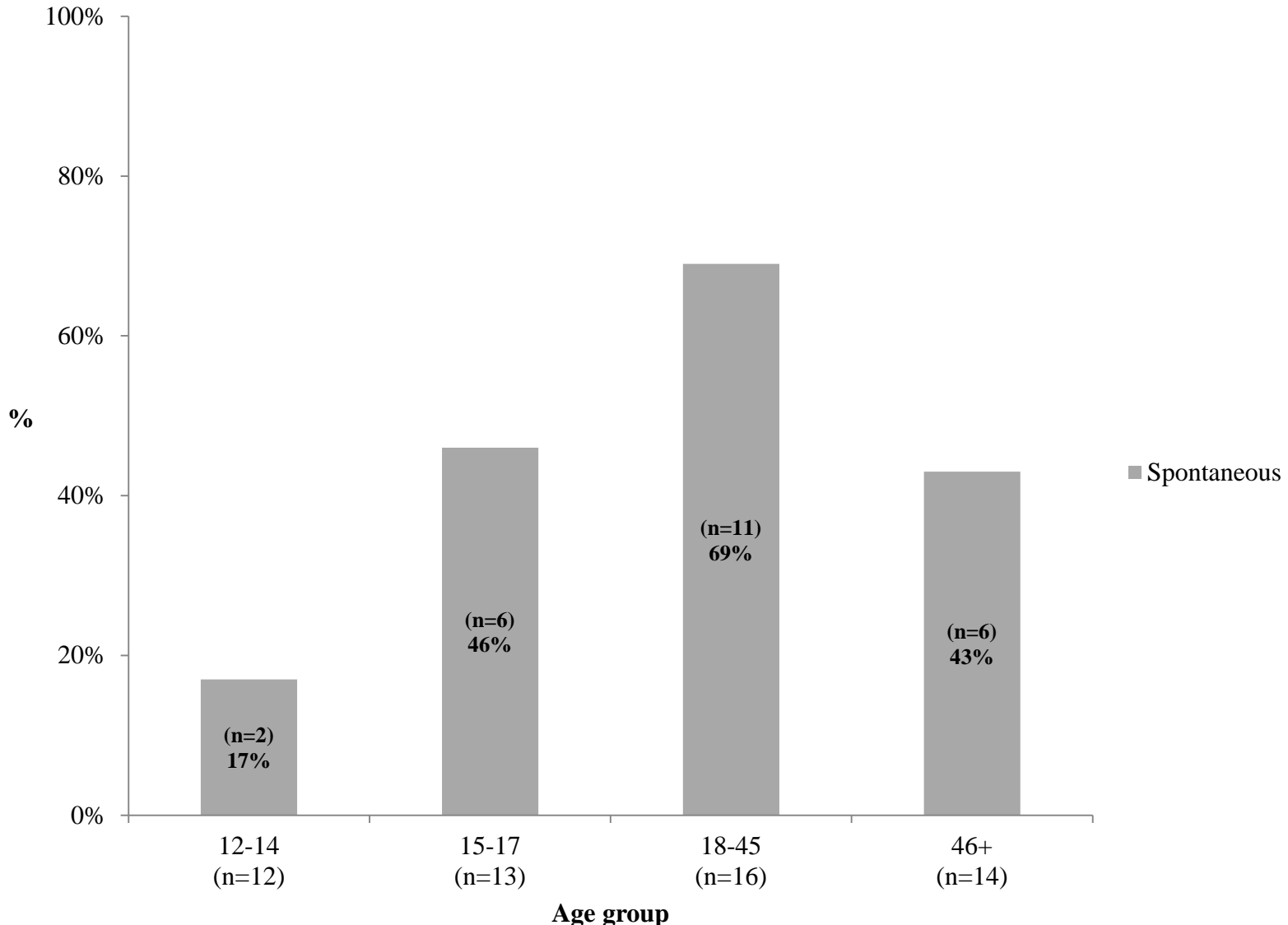
Experience of the disease/concept elicitation in children

- If evidence provided by the caregiver and the child is inconsistent, which is considered the 'gold standard'?
 - Does it depend on age?
- For ObsRO, what if a symptom concept is important but cannot be observed (e.g. chest pain/tightness)?
 - If a parent could rate a symptom based on talking with their child about it, can that be acceptable?
- For verbal children it acceptable to instruct the parent to discuss with their child when completing an ObsRO?
- Alternatively, if the aim is for a rating to be completed based purely on observation, how can we be sure parents will follow those instructions?

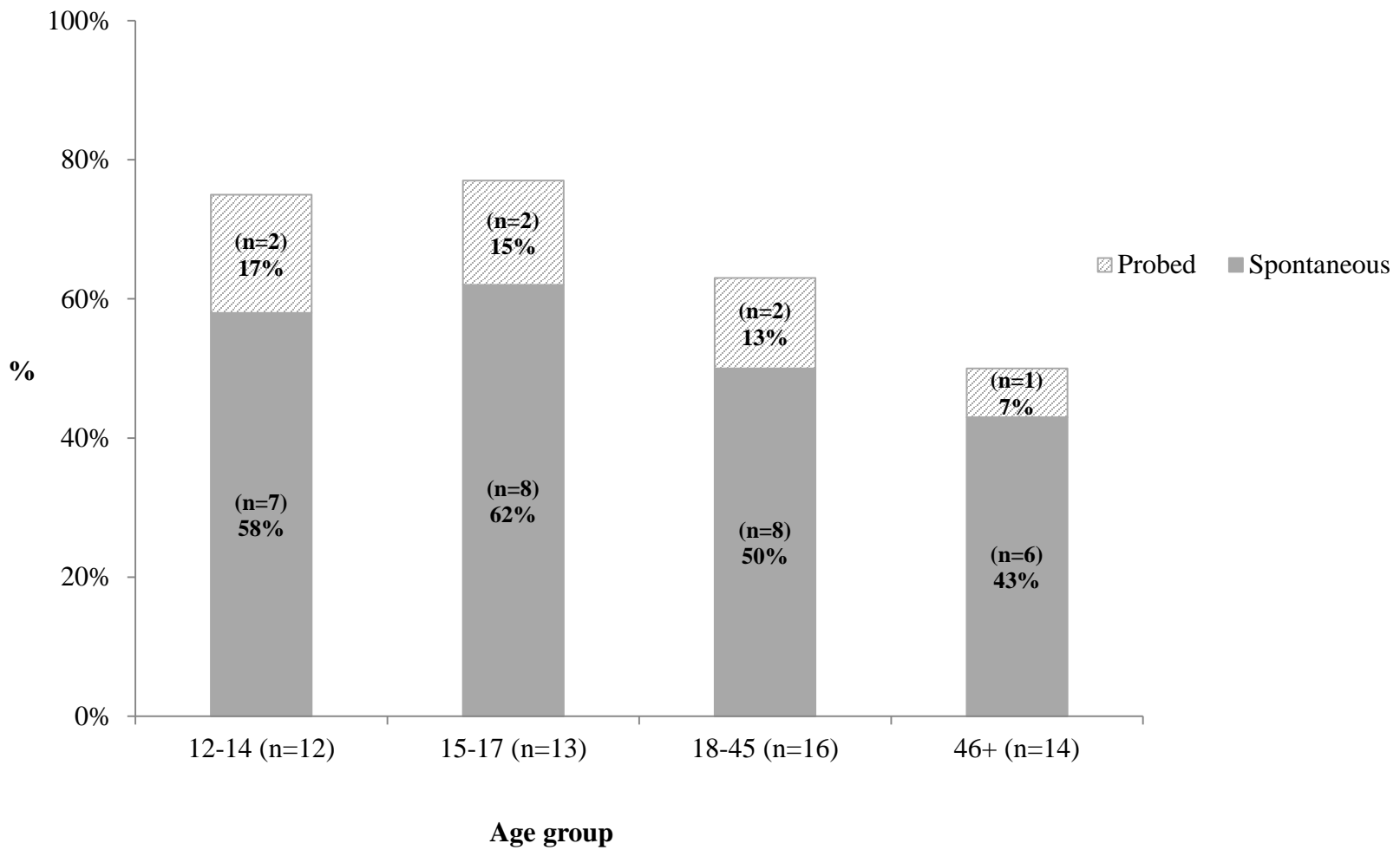
Example: chest tightness reported least often by younger adolescents



Example: chest pressure reported least often by younger adolescents



Example: chest pain reported most often by adolescents



Objectives:

Designing Endpoints for Pediatric Development



Conceptualizing Treatment Benefit

- How do we conceptualize treatment benefit when assessments from different perspectives may be needed?

How do you select a reporter and what questions do you need to consider?

Louis Matza - Evidera

Hari Sachs - FDA

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Determining Who Should Be the Reporter



- Possible reporters: Child, parent (or guardian), teacher, and/or clinician
- The choice among these reporters raises many questions
- How should we determine whether to use child-report or observer-report?
 - Based on age, reading ability, cognitive abilities, clinician judgment, or other criteria?
 - If criteria is based on children's abilities, how to address variation?

Multiple Reporters?

- When would you use multiple reporters (e.g., child and parent)?
- Should multiple reporters be asked about the same construct or different constructs?
- When using multiple reporters, should one be specified as primary?
- Should data from multiple reporters ever be integrated in the analyses?
- How should we interpret data when reporters contradict each other?

- Is it ever acceptable for the reporter to change throughout a trial?
- What to do with children who spend part of the week with one parent and part with another?
- Is it acceptable for the reporter (parent/caregiver) to talk to the child about their symptoms before or during measure completion?
- What about “team completion” with a parent and child working together to respond as a dyad?

Informant-Reported Measures: Observability



- The FDA has stated a preference for informant-reported measures that focus on directly observable content. Are exceptions ever acceptable?
- For example, can a parent ever respond based on information provided by other adults (e.g., the other parent, a teacher, the child)?
- How does the parent complete a diary if they have not seen much of the child that day?
- Can a parent ever provide information on “difficult to observe” content, including school functioning and social functioning?
- Would we be sacrificing content validity if we exclude important, but non-observable content?

Objectives:

Designing Endpoints for Pediatric Development



Selecting/Developing
The Measure



Endpoint
Development

- As disease experience might vary according to developmental age, is it feasible and even suitable to achieve consistency in endpoint concepts in pediatric asthma trials?
 - How can a sensible, feasible endpoint incorporating patient and observer information be constructed?
 - How can we ensure that treatment benefit is assessed using endpoints that are conceptually equivalent across ages?

How do we construct endpoints to support treatment benefit claim across age ranges?

Laura Lee Johnson - NIH

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Yes probably, but it requires lots of qualitative research too



- Plan with the end in mind
 - Why not plan for pediatrics and adapt for adults
 - Think Sesame Street
- Conceptually equivalent or matching text
 - Focus on a common metric for score interpretation
 - Linking scores via universally relevant or ‘generic’ instruments
 - Many COAs are ‘conceptually’ similar
 - PROsetta Stone
 - Hybrids

Do concepts differ across the age ranges? Focus first on similarities



- No differences!
 - Then we ‘just’ need to figure out how to ask the questions and link the scores
 - Qualitative and Quantitative ways to handle this
- Yes
 - Can unification occur?
 - Yes; see above
 - If not, are the differences critical? Does it matter?
 - If so, still there may be some concepts that can be unified, and others that are not
 - If the differences are not critical, if the general outcomes is ok enough and relevant without covering that differing concept, the general outcome might be fine

Good Enough, Reasonably Relevant, Interpretable, Efficient



- Remain open minded
- Start by thinking of the entire life span
- Observable and self-reportable information
- Who needs ObsRO
 - Not only pediatrics
 - Plan for that in initial development
- Are symptom items more similar across the life span than questions about impact?

Open Discussion

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Wrap Up