Practical Considerations in Implementing a Pediatric COA Measurement Strategy

SIXTH ANNUAL

PATIENT-REPORTED OUTCOME CONSORTIUM WORKSHOP

April 29 - 30, 2015 ■ Silver Spring, MD

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Session Outline/Objectives

At the end of this session, participants will be able to:

- summarize key considerations and best practices for patient-focused outcome assessment in a pediatric population;
- describe possible challenges and trade-offs faced when implementing pediatric COAs, as exemplified in a case study involving COAs for pediatric functional constipation; and
- identify practical solutions that are realistic for your patient population and indication, and also respond to the PRO Guidance and ISPOR Task Force recommendations.

Session Participants

Moderator

- Sarrit Kovacs, PhD, Study Endpoints Reviewer, SEALD, FDA

Presenters & Panelists

- Andrew E. Mulberg, MD, FAAP, Division Deputy Director, Gastroenterology and Inborn Errors Products, FDA
- Diane M. Turner-Bowker, PhD, Engagement Leader, Quintiles (previously at ERT)
- Gina Calarco, MPH, BSN, Associate Director, Quintiles Pediatric Center of Excellence
- Jean Paty, PhD, Principal Advisory Services, Quintiles

Agenda

Topic	Presenter	Time (Min)
Introduction	S. Kovacs	2
Regulatory Perspectives on Developing Pediatric COAs	A. Mulberg	10
Case Study in Pediatric Functional Constipation	D. Turner-Bowker	20
Considerations for Implementing COAs in Pediatric Trials	G. Calarco	10
Open Panel Discussion	S. Kovacs	15
Wrap up	S. Kovacs	3

Be a PatientReportedOutcome!
Understanding Children's Needs for Drug Development

Andrew E. Mulberg, MD, FAAP
Division Deputy Director
DGIEP/ODE3/OND/CDER

Disclaimer

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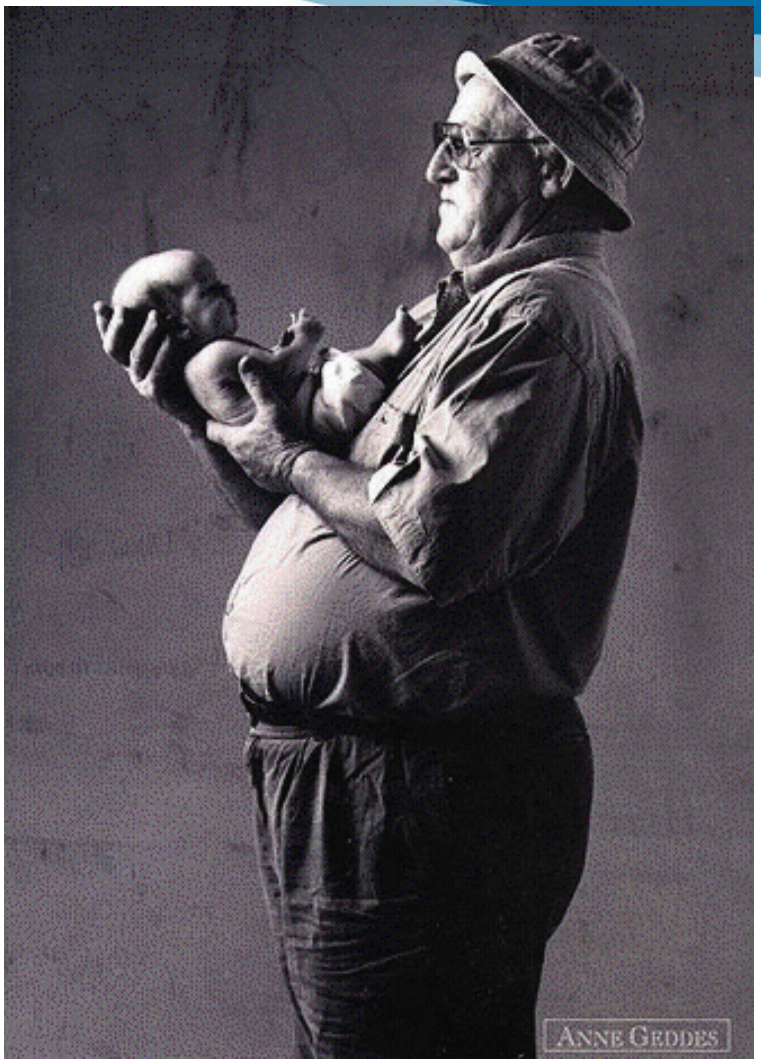
- The presenter has no conflicts of interest or financial relationships with a commercial entity to disclose.

" Pediatrics does not deal with miniature men and women, with reduced doses and the same class of diseases in smaller bodies, but….it has its own independent range and horizon…"

Dr. Abraham Jacobi, 1889



Lessons of this Talk

- Children are an important demographic in drug development
- Goals for Drug Development Programs
  - Define the disease
  - Understand Natural history
  - Develop and identify Clinical Assessment Tools and Outcome Assessments
    - PRO, ObsRO, and/or ClinRO measures
- PPI and infant GERD: An example
  - Understand the importance of having a disease definition
    - GER≠GERD
    - Does disease exist in the age cohort under study?
    - Assumption that adult signs and symptoms are transferable to the pediatric population

Demographics

- **USA: By 2003, there were 73 million children aged 0-17 in the US, or 25% of the population, down from a peak of 36% at the end of the baby boom (1964).**
  - **This proportion is expected to decline only slightly to 24% by 2020**
- **WORLD: Children under age 15 were 29% of a world population pegged at 6,555,000,000 in mid-2006 growing to 7,940,000,000 in 2025**

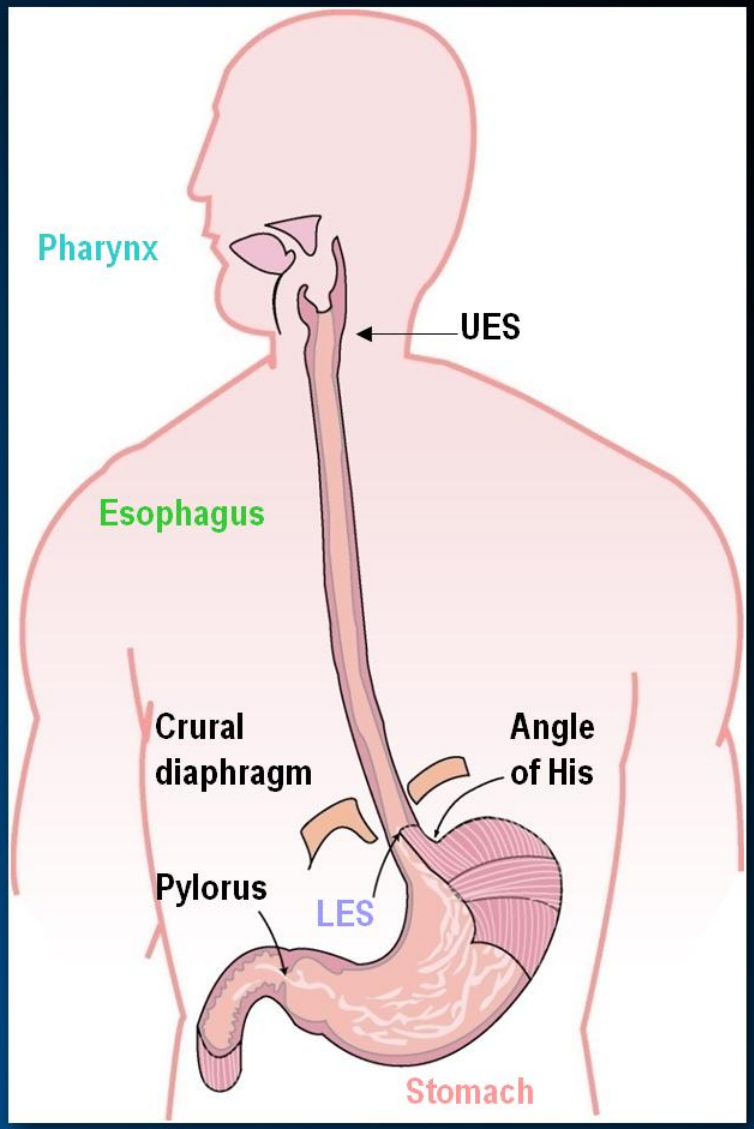
Chris Milne; *Pediatric Drug Development: Concepts and Applications.* Editor: Andrew E. Mulberg et al, Wiley Blackwell, 2009.

Cross-Sector Sponsorship of Research in Eosinophilic Esophagitis: A Collaborative Model for Rational Drug Development in Rare Disease

Robert Fiorentino, Gumei Liu, Anne R. Pariser and Andrew E. Mulberg , JACI 2012

	Define Disease	Assess Natural History	Identify Assessment Tools
Rare Diseases	**Determine Target Population** Include criteria to define clinical trial population **Recognize Stakeholders** Initiate Collaboration **Identify Impeding Factors** Address gaps in knowledge	**Collaborate Among Stakeholders** Survey available resources Plan for longitudinal study **Standardize Data Entry** Use disease specific terminology **Describe Full Disease Spectrum** Distinguish disease subtypes Identify patient subpopulations	**Develop Clinical Outcome Assessment (COA)** Develop patient/clinician/parent reported outcome measures Select clinical endpoints **Evaluate Biomarkers**
EoE	**Define EoE** **Unify Diagnostic Criteria** Use symptomatic and histological criteria **Invite All Stakeholders** Discuss overall plan **Identify Key Issues** Lack of well-defined and reliable COA	**Assess EoE Natural History** **FDA and Academia Collaboration** Pool multiple patient registries **Standardize Data Entry** Interpret data from different sources **Recognize EoE Subpopulation** Define differences between pediatric and adult patients	**Identify EoE Assessment Tools** **Address the Importance of EoE-Specific COAs** Raise questions on using general terms, such as dysphagia Identify the need for different COAs for pediatric and adult patients **Evaluate Intraepithelial Mucosal Eosinophilia as a Biomarker**

Pathogenic Factors in GERD



Primary Mechanisms of GERD

- Transient LES relaxation
- Impaired esophageal clearance

Secondary Mechanisms of GERD

- Intra-abdominal pressure
- Decreased gastric compliance
- Delayed gastric emptying
- Reduced esophageal capacitance

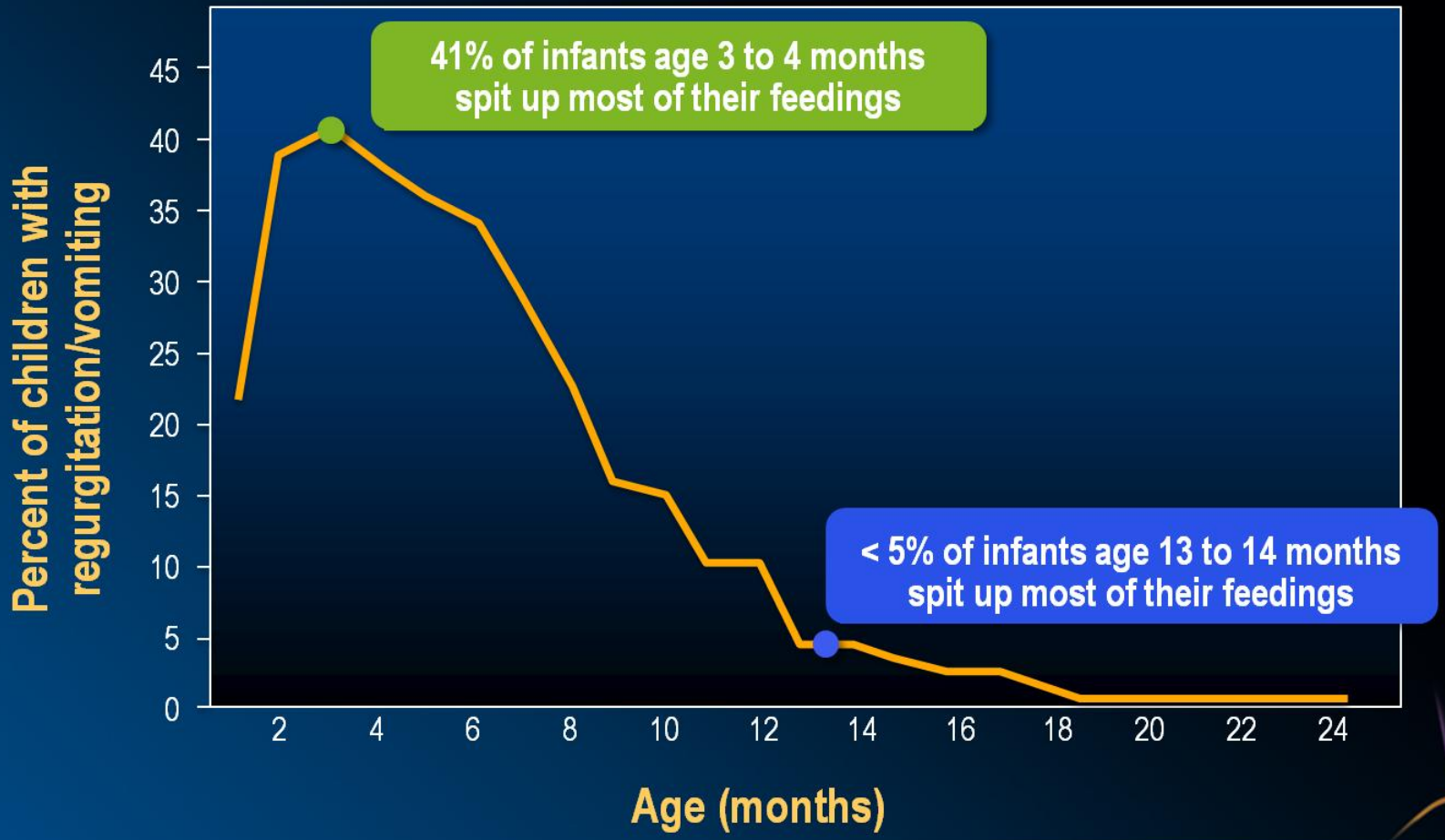
Mechanisms of Esophageal Complications

- Defective tissue resistance
- Noxious composition of refluxate

Mechanisms of Airway Complications (Extra Esophageal Manifestations)

- Vagal reflexes
- Impaired airway protection

Natural History of GER in Children Up to Two Years of Age



Martin et al. *Pediatrics*. 2002;109:1061–1067.

Correlation of Symptoms and Injury

In infants, frequency and severity of symptoms are not reliable to predict the presence or severity of esophagitis.

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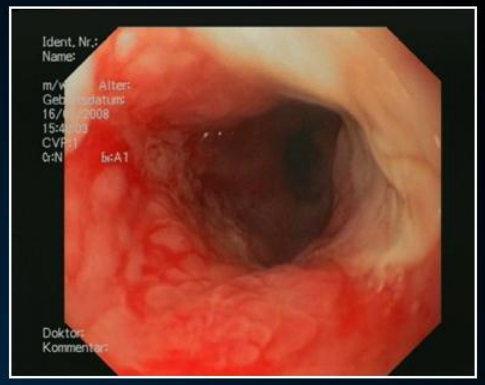

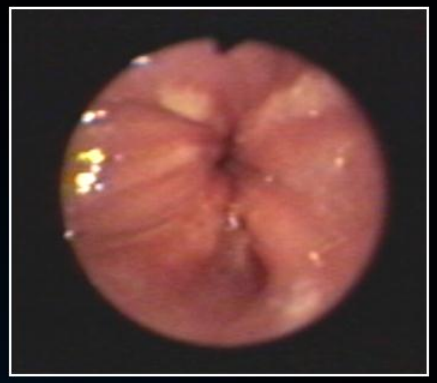

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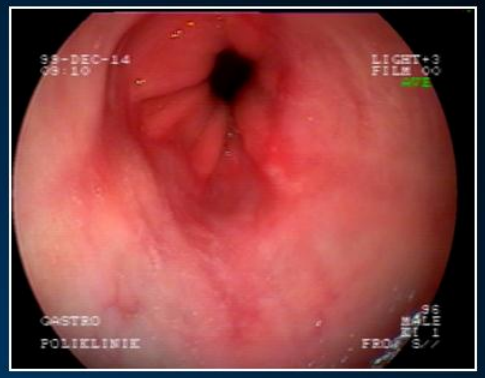
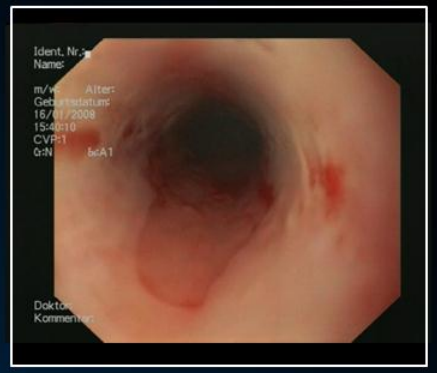
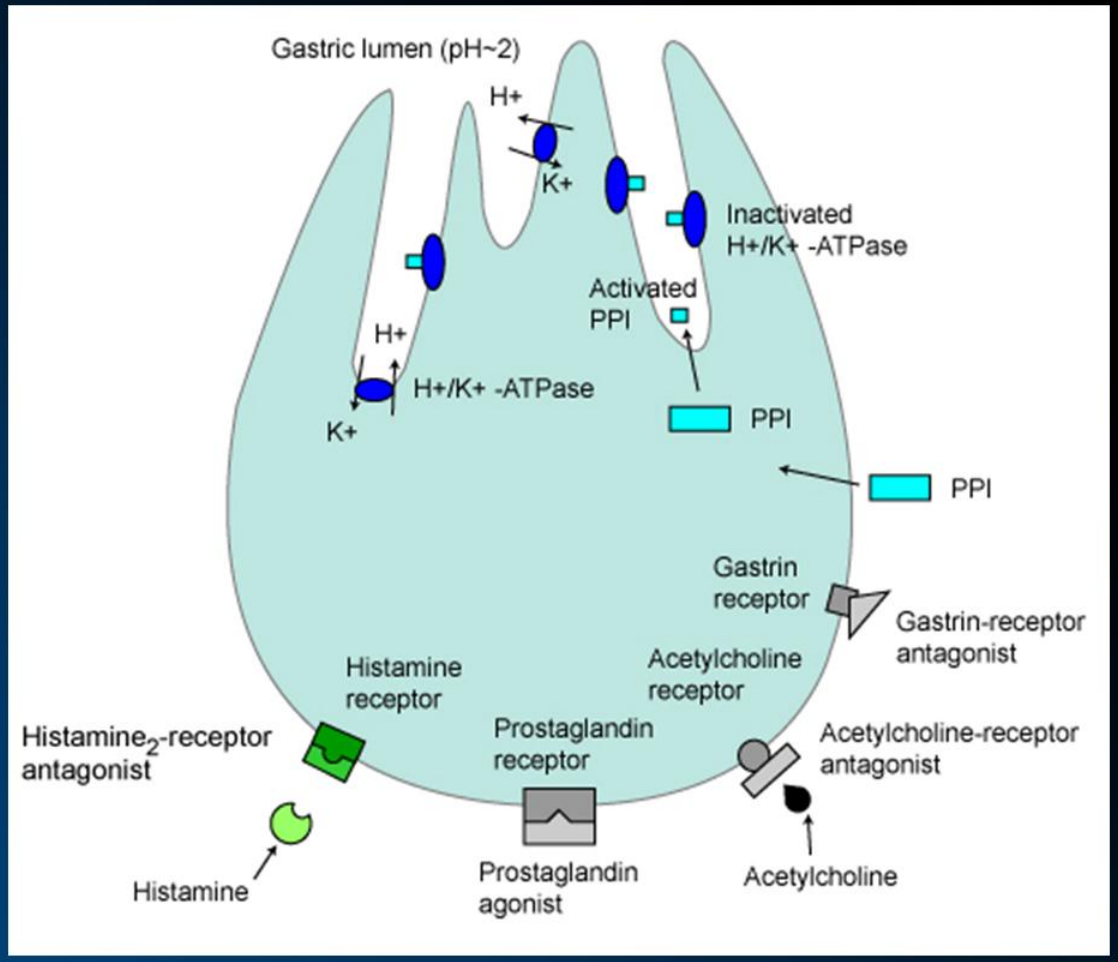




Heine et al. *J Paediatr Child Health*. 2006;42(3):134-9.
Orenstein et al. *Am J Gastroenterol*. 2006; 101(3):628-40.
Salvatore et al. *J Pediatr Gastroenterol Nutr*. 2005;40(2):210-5.

Comparative Summary Clinical Trials of Proton-Pump Inhibitors (PPIs) in Infants (ages 1 to <12 months) with a Diagnosis of GERD

Inhibition of Acid Secretion in the Gastric Parietal Cell



Adapted from Sanders SW, *Clin Therapeutics* 18, 2-34.
Copyright 1996 by Excerpta Medica Inc.

PPI Pediatric Use Trends[1,3] in the Outpatient Setting, 2002-2009

	Year 2002	Year 2009	% Change '02-'09	% Pediatric Share of Total Year 2009
0-17 years old				
Dispensed Prescriptions	875,000	2.6 million	3-fold increase	3%
Patients	332,000	885,000	3-fold increase	5%
<1 year old				
Dispensed Prescriptions	37,000	403,000	11-fold increase	0.5%
Patients	18,000	145,000	8-fold increase	0.8%

[1]SDI, Vector One®: National, Data Extracted May 2010

[3]SDI, Vector One®: Total Patient Tracker, Data Extracted May 2010

Study Population

	Omeprazole	Esomeprazole	Lansoprazole	Pantoprazole
Sample Size	~35/group x 3	~40/group x 2	~80/group x 2	~50/group x 2
Age Range	0 to 24m (90% <12m)	1m to <12m	1m to <12m	1m to <12m
GERD Diagnosis	History of GERD-related symptoms for ≥2m and considered for treatment with acid-reducing agent	History of Suspected, symptomatic or endoscopically-proven GERD	History of Suspected, symptomatic, or endoscopically-proven GERD	History of Suspected, symptomatic, or endoscopically-proven GERD
Screening phase of conservative measures	No	No	Non-response required for randomization	Non-response required for randomization

Study Design

	Omeprazole	Esomeprazole	Lansoprazole	Pantoprazole
Randomized	Yes	Yes	Yes	Yes
Control Group	None	Placebo	Placebo	Placebo
Blinding	Single: patient masked re: treatment group)	Double	Double	Double
Open-Label PPI phase used to sub-select PPI responders	No	Yes, 2 weeks	No	Yes, 4 weeks
Randomized PPI withdrawal	No	Yes	No	Yes
Duration of PPI use in randomized phase	8 weeks	4 weeks	4 weeks	4 weeks

Primary Endpoint

Esomeprazole	Lansoprazole	Pantoprazole	Omeprazole
Time to W/D due to worsening of GERD signs/symptoms	Proportion of patients with ≥50% reduction in frequency or duration of GERD signs/symptoms with feeds	Withdrawal rate due to lack of efficacy (defined by more frequent or severe signs/symptoms, or endoscopy worsening, or prolonged antacid use)	Change in daily average vomiting-regurgitation frequency

Results

RESULTS	Esomeprazole	Lansoprazole	Pantoprazole	Omeprazole
Primary Efficacy Result	HR=0.69 95% CI [0.35, 1.35]	54% response (44/81) (p=1.000)	PPI: 12% (6/52) PLB: 11% (6/54) (p=1.000)	50% reduction in all 3 dose groups (p>0.50)

PPIs Do Not Improve Symptoms in Infants including crying

- **Omeprazole showed no improvement in cry-fuss time over a 24 hour period as compared to placebo in a RCT**
- **Lansoprazole showed no improvement in crying, back arching, wheezing or regurgitation as compared to placebo in a RCT**
- **In preterm infants and neonates esomeprazole produces no change in bolus reflux characteristics despite significant acid suppression**

Orenstein et al J Pediatr 2009;154:514-520, Omari et al J Pediatr 2009;155:222-228, Moore et al J Pediatr 2003; 143:219-223.

Conclusions

- Understand mechanism of action of the drug and its target to the pathophysiology of disease
  - Is it different for infants, children and adolescents?
- Understand the role of extrapolation from adult efficacy
- Why combining endpoints across age groups may influence outcome conclusions
- How some trials are limited to specific age groups

Partnership is the Key

- "Coming together is a beginning; keeping together is progress; working together is success."
  Henry Ford

  http://www.brainyquote.com/quotes/authors/h/henry_ford.html

Practical Considerations in Implementing a Pediatric COA Measurement Strategy:

A Case Study in Functional Constipation

Diane M. Turner-Bowker, PhD

Engagement Leader, Quintiles (previously at ERT)

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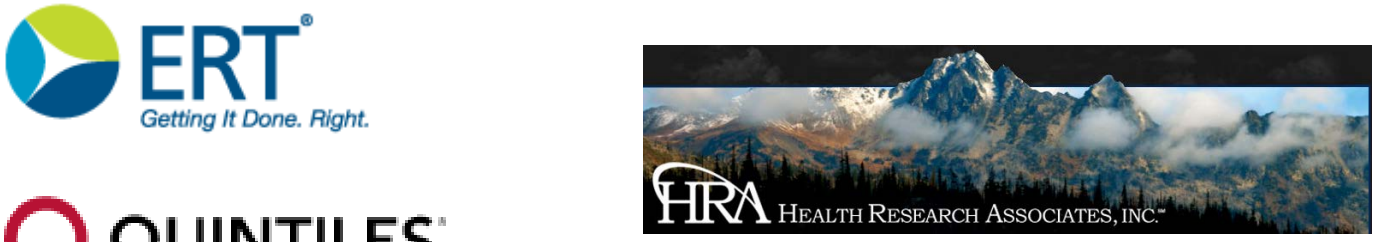
Acknowledgments

- Sucampo Pharma Americas, LLC & Takeda Pharmaceutical Company Limited sponsored this research

- Conducted with a team of scientists at ERT, and in partnership with Health Research Associates and Quintiles.

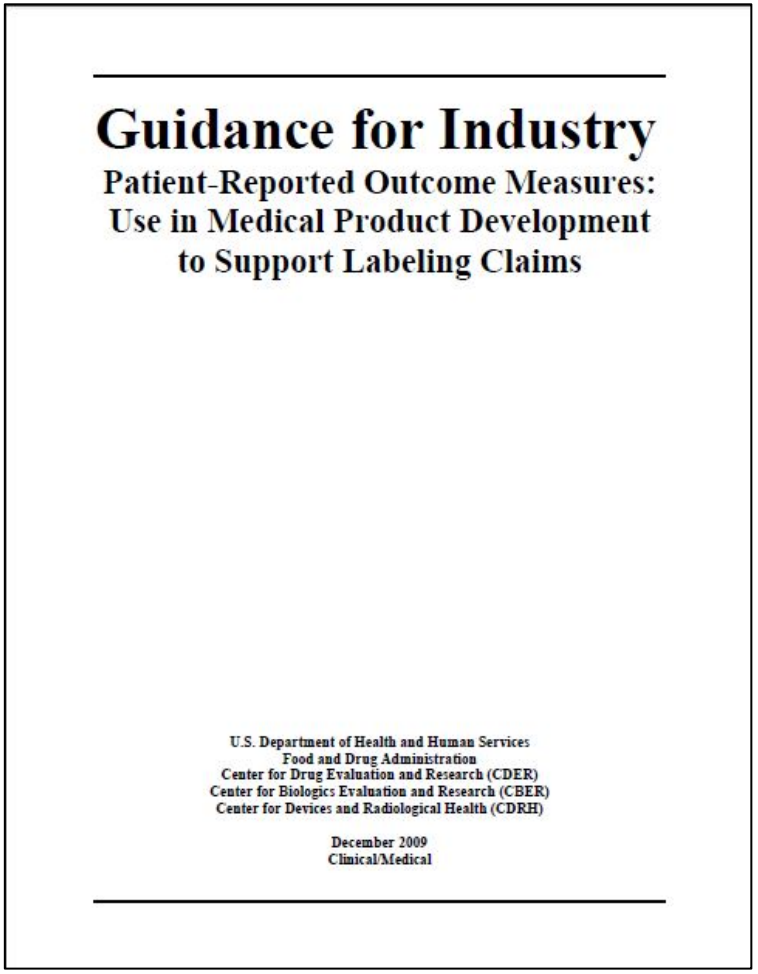


Case Study in Pediatric Functional Constipation

- Background
  - Best practices in pediatric COA development
  - Sucampo's pediatric functional constipation program
- Questions:
  - What challenges did we face in developing COAs for pediatric functional constipation?
    - How did we achieve solutions that were practical and still addressed 'best practice' recommendations? What trade-offs were considered?
  - What impact has this had on our endpoint strategy?
  - What are our next steps?

Best Practices in COA Development for Pediatric Populations

PRO CONSORTIUM
CRITICAL PATH INSTITUTE



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

VALUE IN HEALTH 16 (2013) 483–499

Available online at www.sciencedirect.com
SciVerse ScienceDirect
journal homepage: www.elsevier.com/locate/jval

ISPOR TASK FORCE REPORTS

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

Louis S. Matza, PhD[1,*], Donald L. Patrick, PhD, MSPH[2], Anne W. Riley, PhD, MS[3], John J. Alexander, MD, MPH[4], Luis Rajmil, MD, PhD, MPH[5], Andreas M. Pleil, PhD[6], Monika Bullinger, PhD[7]

[1]Outcomes Research, United BioSource Corporation, Bethesda, MD, USA; [2]Department of Health Services, University of Washington, Seattle, WA, USA; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [4]Division of Anti-Infective Products, FDA, Silver Spring, MD, USA; [5]IMIM-Hospital del Mar Medical Research Institute and Catalan Agency for Health Information, Assessment and Quality, Barcelona, Spain; [6]Pfizer Global Pharmaceuticals, Pfizer, Inc, San Diego, CA, USA; [7]Department of Medical Psychology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

ABSTRACT

Background: Patient-reported outcome (PRO) instruments for children and adolescents are often included in clinical trials with the intention of collecting data to support claims in a medical product label. **Objective:** The purpose of the current task force report is to recommend good practices for pediatric PRO research that is conducted to inform regulatory decision making and support claims made in medical product labeling. The recommendations are based on the consensus of an interdisciplinary group of researchers who were assembled for a task force associated with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). In those areas in which supporting evidence is limited or in which general principles may not apply to every situation, this task force report identifies factors to consider when making decisions about the design and use of pediatric PRO instruments, while highlighting issues that require further research. **Good Research Practices:** Five good research practices are discussed: 1) Consider developmental differences and determine age-based criteria for PRO administration. Four age groups are discussed on the basis of previous research (<5 years old, 5–7 years, 8–11 years, and 12–18 years). These age groups are recommended as a starting point when making decisions, but they will not fit all PRO instruments or the developmental stage of every child. Specific age ranges should be determined individually for each population and PRO instrument. 2) Establish content validity of pediatric PRO instruments: This section discusses the advantages of using children as content experts, as well as strategies for concept elicitation and cognitive interviews with children. 3) Determine whether an informant-reported outcome instrument is necessary: The distinction between two types of informant-reported measures (proxy vs. observational) is discussed, and recommendations are provided. 4) Ensure that the instrument is designed and formatted appropriately for the target age group: Factors to consider include health-related vocabulary, reading level, response scales, recall period, length of instrument, pictorial representations, formatting details, administration approaches, and electronic data collection (ePRO). 5) Consider cross-cultural issues. **Conclusions:** Additional research is needed to provide methodological guidance for future studies, especially for studies involving young children and parents' observational reports. As PRO data are increasingly used to support pediatric labeling claims, there will be more information regarding the standards by which these instruments will be judged. The use of PRO instruments in clinical trials and regulatory submissions will help ensure that children's experience of disease and treatment are accurately represented and considered in regulatory decisions.

Keywords: adolescents, children, ISPOR, medical product labeling, patient-reported outcomes, pediatrics, PRO, task force.

* Address correspondence to: Louis S. Matza, United BioSource Corporation, 7101 Wisconsin Avenue, Suite 600, Bethesda, MD 20814, USA.
E-mail: louis.matza@unitedbiosource.com.

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http://dx.doi.org/10.1016/j.jval.2013.04.004

Best Practices in COA Development for Pediatric Populations (cont.)

#1 Consider developmental differences and determine age cutoffs

#2 Content validity

#3 Determining if an informant-reported outcome is necessary

#4 Instrument should be designed/formatted appropriately for target age group

#5 Consider cross cultural issues

Developing a Pediatric COA Measurement Strategy: A Case Study in Asthma, Fifth Annual PRO Consortium, April 29-30, 2014.

Matza LS, Patrick DL, Riley AW, Alexander JJ, Rajmil L, Pleil AM, Bullinger M. 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. 2013 Jun;16(4):461-79.

Best Practices in COA Development for Pediatric Populations (cont.)

*"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."*

Developing a Pediatric COA Measurement Strategy: A Case Study in Asthma, Fifth Annual PRO Consortium, April 29-30, 2014.

ISPOR Pediatric Task Force Paper
(Matza et al., 2013)

Pediatric PRO assessment…

*"is a **developing field** of research, and empirical evidence **is limited** for some important areas of instrument design, development, validation, and implementation."*

Sucampo Pharma Americas, LLC: Pediatric Functional Constipation

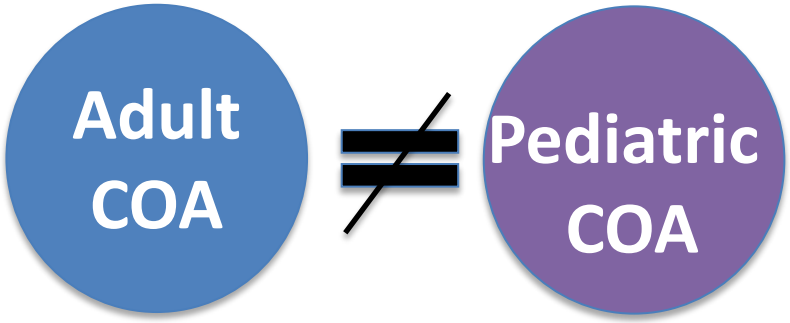
- ERT is working with Sucampo to develop 'fit for purpose' COAs
  - children ages 6 months to < 6 years
  - children/adolescents ages 6 years to <18 years
- Sucampo was approaching Phase 3 with an initial plan to modify adult COA instruments for use with children
- How to implement best practice recommendations in this context?
  - Best practice sources provide goals and guidelines, not detailed solutions
  - Examples of practical, reasonable, acceptable solutions are needed

What key challenges did we face in implementing COAs for pediatric functional constipation?

- **Data collection approach**
  - eDiary will be used
  - How to select a reporter?
    - Who will be responsible for eDiary completion on a daily basis?
    - Who will complete the items (patient and/or parent)?
- **Limited timeline**
  - How to develop/modify items and gain 'fit for purpose' evidence in very short timeline?
- **Patient population with wide age span**
  - Do the same key concepts apply across patients of different ages? If not, how will this affect the endpoint strategy?

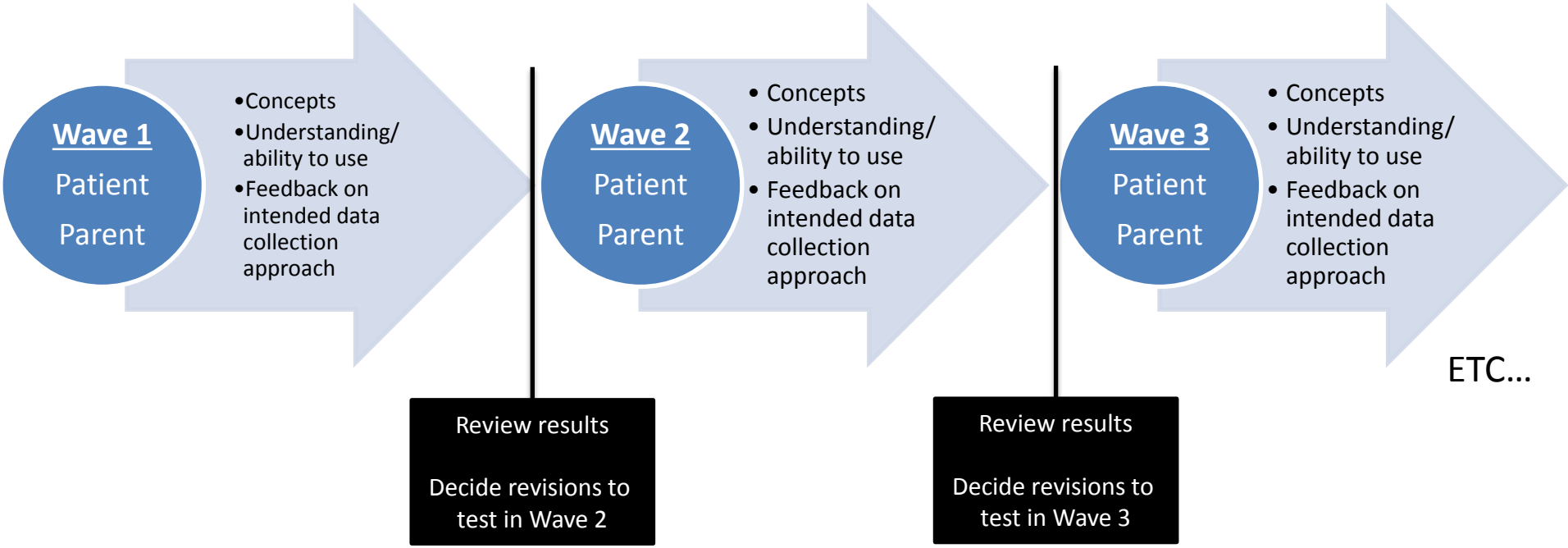
How did we achieve solutions that were practical yet align with ‘best practice’ recommendations?

Limited Timeline



- Modify existing items / develop new items
- Combined concept elicitation/cognitive testing patient/legal guardian interviews
- Measurement properties evaluation as part of Phase 3

Combined Patient/Parent CE/Cognitive Interviews



Data Collection Approach

- Data collection approach
  - eDiary will be used
  - How to select a reporter?
  - Who will complete the eDiary on a daily basis?
  - Who will complete the items (patient and/or parent)?

Considerations for Data Collection

- **What data collection mode and schedule will be used, given indication and project needs?** **DAILY eDIARY**
  - Project requires daily assessment of key concepts (e.g., BM)
- **Will an informant report needed?** **YES**
- **Who will have primary responsibility for eDiary completion?** **PARENT**
  - Determined that it was not practical to make data entry a fully shared task.
  - If 2 people are responsible for daily data entry, may find compliance and data quality issues (e.g., no single person responsible for the daily task, too many hand offs).
  - Given the wide age range of children in the study (6 mo to < 18 years), decided that the parent should 'own' this responsibility – to standardize our approach across the age range.
- **Who will complete the items?**
  - Parents reported on ObsRO; children/adolescents reported on PRO (few items).
  - Would children/adolescents feel uncomfortable with their parent reporting BMs? NO ….
    - Evaluated this in qualitative interviews with parents, children/adolescents
    - Thus far, no reported concerns with this from parents/children in ongoing trial (quantitative measurement properties)

Do the same key concepts apply across patients of different ages?

- Targeted representation by age group
- Children/Adolescents ages 6 to <18 years
  - Parent and child ages 6-7
  - Parent and child ages 8-12
  - Parent and child ages 13-17
- Parents of Children ages 6 months to < 6 years

How did it work?

- **Combined interviews worked well** (~ 90 min each)
- **More waves than anticipated**, due to recruitment and scheduling logistics for this sample; however, this provided an unexpected benefit (more opportunity to consider and test item additions/revisions).
  - E.g., 'hard abdomen' – emerged early as possible predominant concept; we tested this as an additional item, and found it was relevant to younger children, not older group
- **Achieved saturation** of content for older and younger groups

How did it work? (cont.)

- **Most concepts were similar across age groups** – especially predominant signs/symptoms and impacts
  - We ask what parents have observed; however, parents do not distinguish between signs and symptoms.
    - For example, parents will often say, 'My child has pain." Probing follow up questions assess observations that caused the parent to draw this conclusion.
- Based on these results **our endpoint strategy (primary, key secondary) may not differ** notably for older and younger children.

How did it work? (cont.)

- PRO and ObsRO **items were generally well understood**
  - Some children can read but not comprehend
  - Some children cannot read but CAN comprehend (e.g., parent read instructions; interviewer administered)
    - E.g., Modified Bristol Stool Form Scale for Children
      - Because several of the younger children had difficulty due to low reading ability, a recommendation was made for the parent/legal guardian to read instructions and item text to children 10 years and younger (child independently decides upon and selects a response).
      - This approach is consistent with published literature on the mBSFS-C [Lane et al 2011].
  - Some children understand and are capable of responding, but need to feel 'at ease' in order to do so

Summary

- Innovative approaches to design
- Methodological decisions necessary considering developmental stage
  - (e.g., age, reading ability, memory, interpersonal/willingness to participate, etc.)
    In preparation for / In response to
- Trade-offs – no single solution may be best
- Practical and flexible
- Important considerations for endpoint strategy
- Next step – measurement properties evaluation
- Share findings – our community

Pediatric considerations for planning and executing clinical outcome assessments within a clinical trial

Gina Calarco, MPH, BSN, RN, CCRC
Associate Director, Deputy Head
Pediatric Center of Excellence, Quintiles

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Overview of Pediatric CT

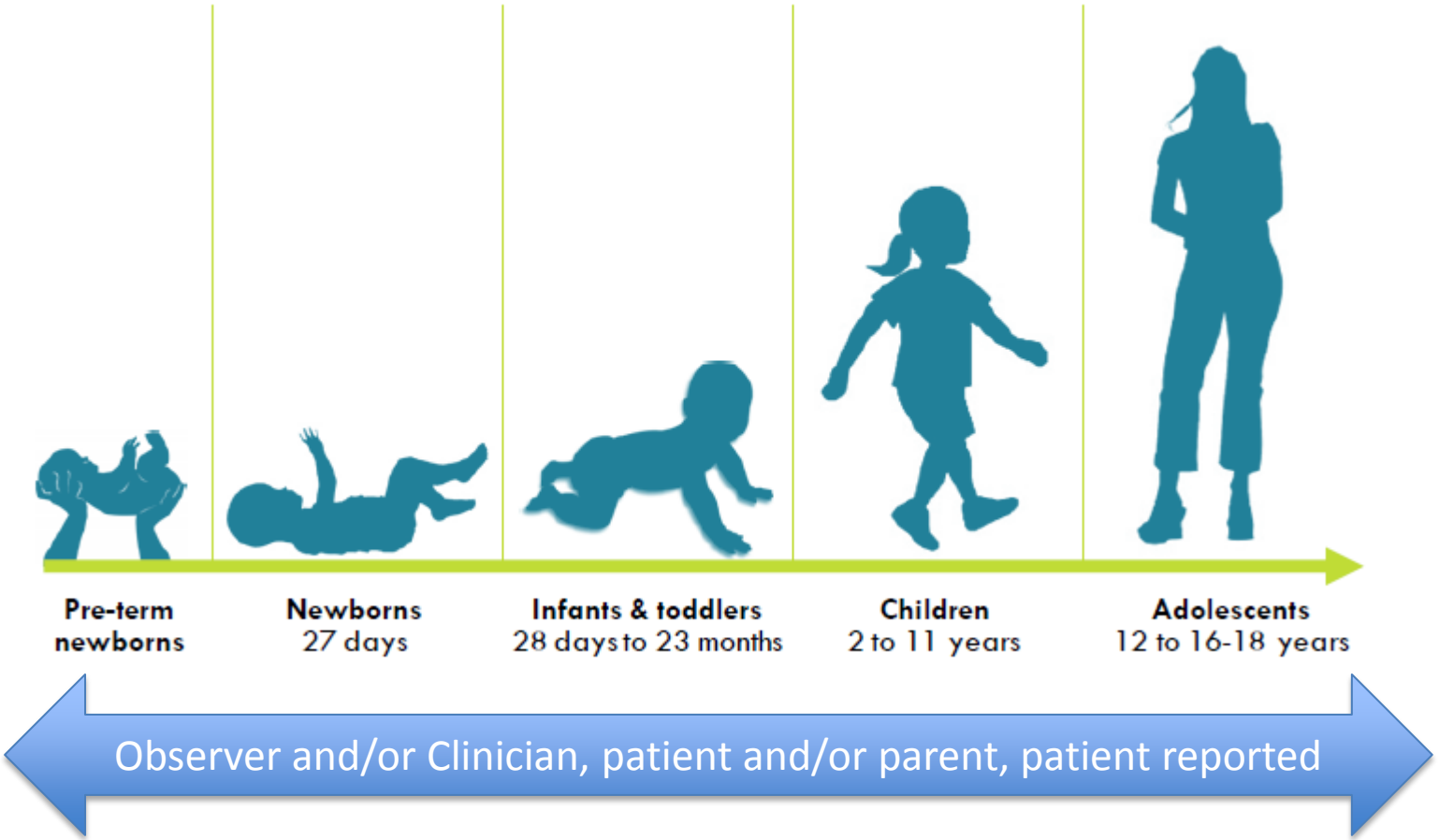
- Increased focus and need for Pediatric clinical trials
  - Regulatory mandates
  - Added exclusivity for sponsors
- Pharma working from a predominately adult clinical trial focus and experience set
  - US: pediatric trials are mandated shortly after Phase II adult studies begin
  - EU: Pediatric Investigational Plan (PIP) required after adult PK data in and prior to Phase II starting

PRO Pediatric Considerations

- Pediatric limitations:
  - Memory/recall
  - Vocabulary
  - Attention span
  - Ability to understand complex sentences
  - Ability to read/write
  - Effect of presence of caregiver, parent, clinician
  - Impact of parent's notions of disease state and child's reaction(s)
  - Rare conditions and small patient populations

- Limitations and strategy vary greatly depending on age, disease, culture

Considerations by Age



- FDA guidance document and ISPOR advises against proxy
- No good data or guidance on when a child can self report
- Developmentally children differ dramatically and disease states can affect this

Real life planning/development - Suboptimal strategies

- Pediatric clinical development often based upon the adult clinical program
- Pediatric PRO tool selection and use
  - Pulled from adult studies and utilized
  - Proxy reporting used with existing instruments
  - Limited to no qualitative research done to establish concepts and patient understanding to guide for further PRO tool development
  - Quick Internet or article searches for a tool

When problems arise

- Problems usually arise AFTER the protocol has been finalized
  - KOLs may not have been advised on COA tool
  - CRO review of protocol and COA tool
  - Sites question use, feasibility, or understanding of COA tool
  - Training on COA tool results in questions
    - Site, parent, subject

How can we do better?

- Early collaboration is key!
  - During early clinical development
  - Work with advocacy groups, KOLs, CRO experts, consortiums, parents/caregivers, and pediatric patients
  - Specific COA tools developed based on the study needs if no other tool exists
    - Qualitative research done to assess most important outcome(s) to be measured and to support further development of a valid, reliable and context appropriate COA tools
    - Pharma or collaborative efforts to invest time and expense for better outcome measures
- Use of technology
  - iPads, phones, activity trackers, etc.

Take Home Points

- Further testing of adult tools within pediatrics and/or development of pediatric specific COA tools needs to happen for quality data
- EARLY Collaboration is essential

Open Panel Discussion

Questions & Answers

Session Participants

Moderator

- Sarrit Kovacs, PhD, Study Endpoints Reviewer, SEALD, FDA

Presenters & Panelists

- Andrew E. Mulberg, MD, FAAP, Division Deputy Director, Gastroenterology and Inborn Errors Products, FDA
- Diane M. Turner-Bowker, PhD, Engagement Leader, Quintiles (previously at ERT)
- Gina Calarco, MPH, BSN, Associate Director, Quintiles Pediatric Center of Excellence
- Jean Paty, PhD, Principal Advisory Services, Quintiles

Thank You!