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

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

- The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to FDA as the organization with which the presenter is employed or affiliated.
- 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
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
- Determine Target Population
  - Include criteria to define clinical trial population
- Recognize Stakeholders
  - Initiate Collaboration
- Identify Impeding Factors
  - Address gaps in knowledge

Assess Natural History
- 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

Identify Assessment Tools
- Develop Clinical Outcome Assessment (COA)
  - Develop patient/clinician/parent reported outcome measures
  - Select clinical endpoints
  - Evaluate Biomarkers

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

41% of infants age 3 to 4 months spit up most of their feedings

< 5% of infants age 13 to 14 months spit up most of their feedings

Correlation of Symptoms and Injury

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

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 Trends¹,³ in the Outpatient Setting, 2002-2009

<table>
<thead>
<tr>
<th></th>
<th>Year 2002</th>
<th>Year 2009</th>
<th>% Change '02-'09</th>
<th>% Pediatric Share of Total Year 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0-17 years old</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispensed Prescriptions</td>
<td>875,000</td>
<td>2.6 million</td>
<td>3-fold increase</td>
<td>3%</td>
</tr>
<tr>
<td>Patients</td>
<td>332,000</td>
<td>885,000</td>
<td>3-fold increase</td>
<td>5%</td>
</tr>
<tr>
<td><strong>&lt;1 year old</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispensed Prescriptions</td>
<td>37,000</td>
<td>403,000</td>
<td>11-fold increase</td>
<td>0.5%</td>
</tr>
<tr>
<td>Patients</td>
<td>18,000</td>
<td>145,000</td>
<td>8-fold increase</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

¹SDI, Vector One®: National, Data Extracted May 2010  
³SDI, Vector One®: Total Patient Tracker, Data Extracted May 2010
## Study Population

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

<table>
<thead>
<tr>
<th></th>
<th>Omeprazole</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Pantoprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Control Group</td>
<td>None</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Blinding</td>
<td>Single: patient masked re: treatment group)</td>
<td>Double</td>
<td>Double</td>
<td>Double</td>
</tr>
<tr>
<td>Open-Label PPI phase used to sub-select PPI responders</td>
<td>No</td>
<td>Yes, 2 weeks</td>
<td>No</td>
<td>Yes, 4 weeks</td>
</tr>
<tr>
<td>Randomized PPI withdrawal</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Duration of PPI use in randomized phase</td>
<td>8 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>
## Primary Endpoint

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

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

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

[link](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?
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 Biologic Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009

Clinical/medical
#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


“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.”

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.”
• 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

Wave 1 Patient/Parent
- Concepts
- Understanding/ability to use
- Feedback on intended data collection approach

Wave 2 Patient/Parent
- Concepts
- Understanding/ability to use
- Feedback on intended data collection approach

Wave 3 Patient/Parent
- Concepts
- Understanding/ability to use
- Feedback on intended data collection approach

Review results
Decide revisions to test in Wave 2

Review results
Decide revisions to test in Wave 3

ETC...
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
• **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.
• 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

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– Gina Calarco, MPH, BSN, Associate Director, Quintiles Pediatric Center of Excellence
– Jean Paty, PhD, Principal Advisory Services, Quintiles
Thank You!