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

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Based on the Work of a Recent ISPOR Task Force

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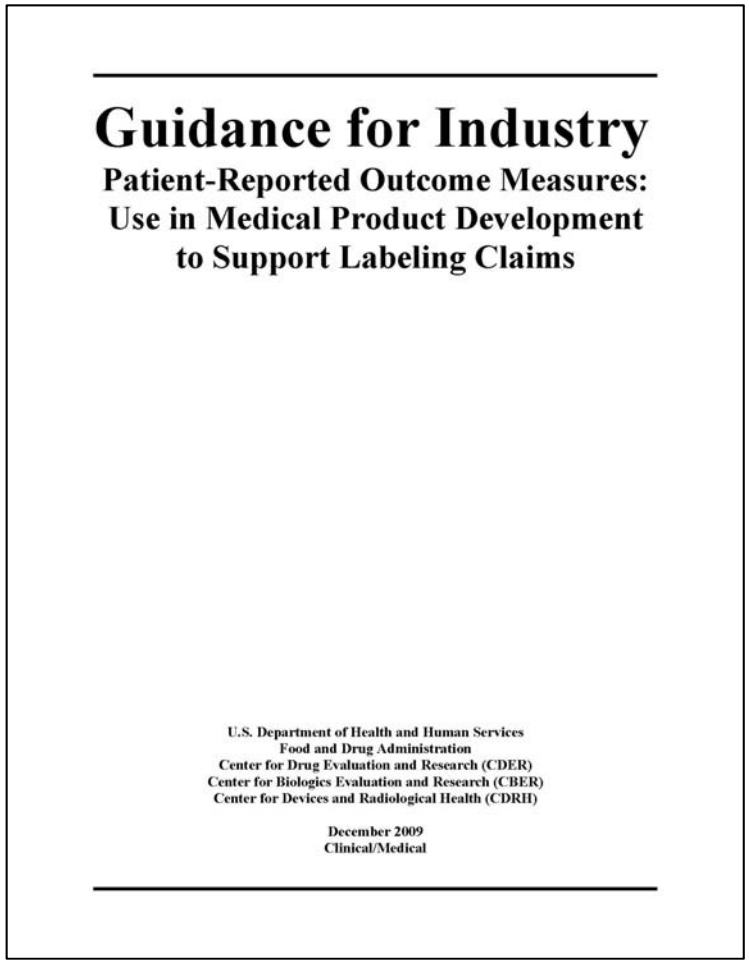
Background



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)

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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

Developmental Appropriateness

- **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

- 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	• Must rely on informant-report.
5-7	Marginal	• More research is needed. • Child-Report appears unlikely to yield results acceptable for regulatory decision-making.
8-11	Varies, but often acceptable	• 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	• 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 should be conducted to examine whether the instrument is appropriate for the target age group.
  - Quantitative research can be conducted 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

Content Validity

- 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

Concept Elicitation for a New Pediatric Instrument

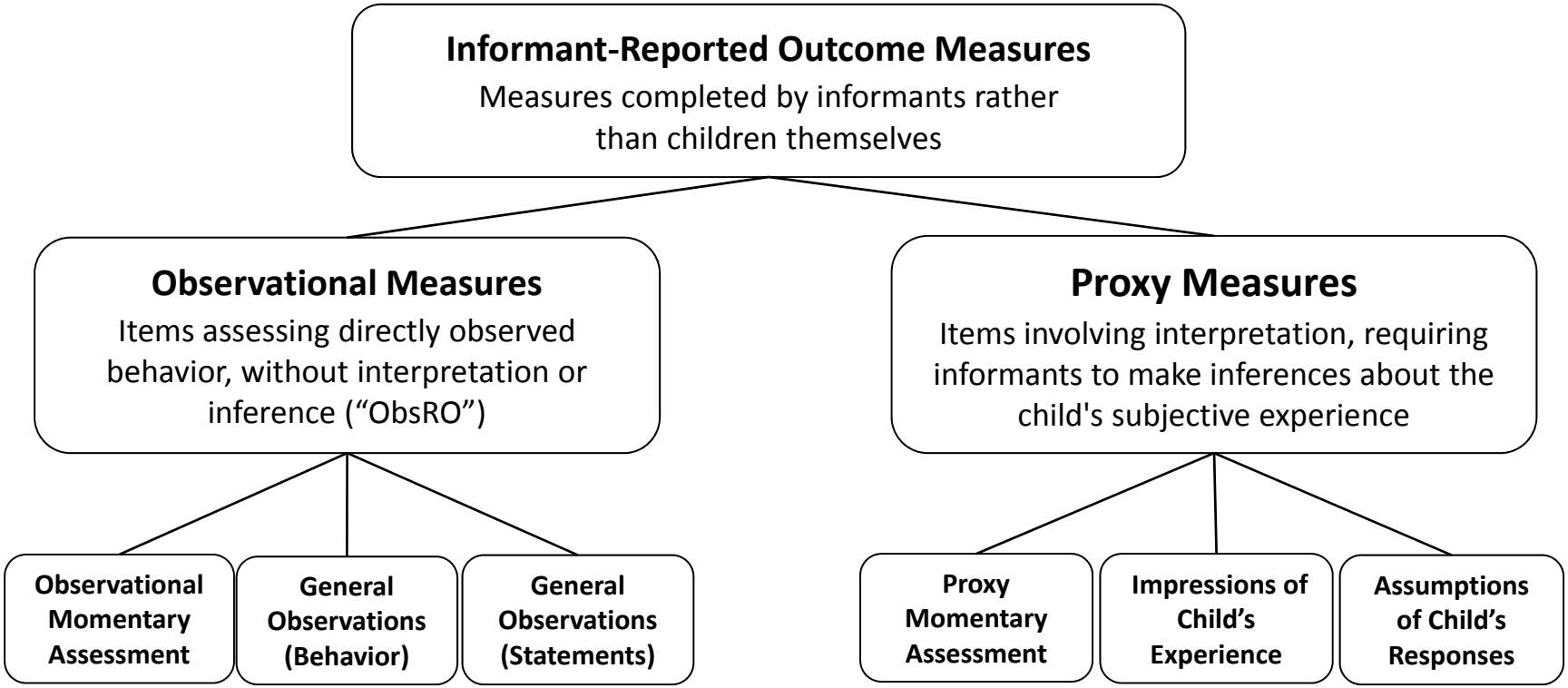
- Children and adolescents can be effective content experts
- Data may be gathered in interviews or focus groups.
- We recommend interviewing several types of respondents, including the children themselves, parents, and clinicians.
- Children should be included in the early stages of establishing content validity, particularly when developing a child-report instrument.

Cognitive Interviews

- 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



Proxy Versus Observational Measures

- 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.

Three Recommendations for Informant-Reported Outcomes in Research for Medical Product Evaluation and Labeling

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.

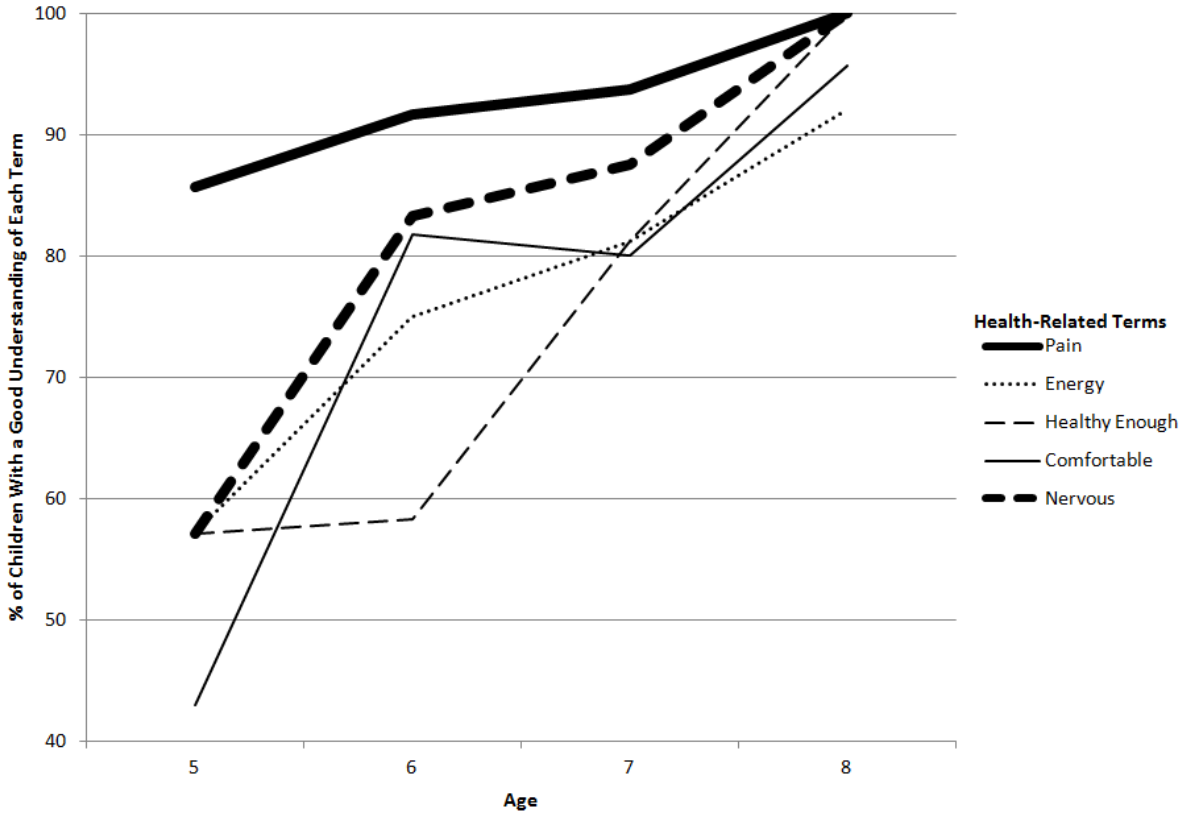
Good Practice 4:
Ensure that the Instrument is Designed and Formatted Appropriately for the Target Age Group

Age-Appropriate Instrument Design and Format

- In the task force manuscript, we discuss issues that must be considered to ensure that a PRO instrument is developmentally appropriate for the age range of a pediatric sample.
- 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.

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



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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

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.**

Conclusions

- 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 intention of this task force was to present general guidance and discuss the important 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.