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COMMENTARY

Advancing Pediatric Patient-Reported Outcome Assessment

The biomedical research community has made great strides toward jettisoning the notion that "children are little adults." It is now well recognized that children's unique patterns of health and disease, growth and development, and dependency on adults for managing their health provide strong justification for the field of pediatric research [1]. The types, manifestations, and frequency of various diseases as well as the adverse event profile for medical treatments can differ between adults and children, and sadly conditions such as hypertension and metabolic syndrome once considered adult-onset have infiltrated childhood. Maturation of children's physiology influences the qualitative and quantitative effects of medical products, which calls into question the use of "hand-me-down" [2] results from medical product studies done among adults. Particularly for infants and young children we rely on parents and caregivers to implement treatments and to provide their observations on treatment effects.

Recognition of the unique attributes of childhood that merit a special research focus is relatively new. A 1996 workshop held jointly by the American Academy of Pediatrics and the National Institute of Child Health and Human Development concluded that approximately 15% of research studies had inappropriately excluded children. This deficiency was a key reason why the National Institutes of Health issued guidelines in 1998 on the inclusion of children in clinical research [3]. At about the same time, Congress passed the Food Drug Administration Modernization Act that offered an additional 6 months of market exclusivity to pharmaceutical companies for conducting pediatric studies [4]. Many drugs continue to receive pediatric labeling under this provision. Today, the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act provide a regulatory infrastructure comprising incentives and requirements intended to increase the amount of medical product research done on children and adolescents [5].

During the same interval that children in clinical studies were receiving more attention, the use of patient-reported outcomes (PROs) in research proliferated. The 2009 guidance issued by the Food and Drug Administration on necessary criteria for using PROs to support medical product labeling [6], the federal government's establishment of the Patient-Centered Outcomes Research Institute [7], and the National Institute of Health's Patient Reported Outcome Measurement Information System [8] are important accelerators for the adoption of PROs into the clinical research enterprise. New guidelines for selecting PROs [9] and reporting PRO results [10] have been produced to strengthen the quality of the rapidly growing knowledge base that has accrued as a result of the inclusion of PROs in studies.

Anticipating the dual trends in greater pediatric clinical research and use of PROs as clinical end points, ISPOR convened an expert panel to develop best practice recommendations for using pediatric PROs in medical product labeling [11]. The authorship team responsible for these good research practices has produced a tour de force. Nowhere else in the literature can a reader find such a detailed compendium of evidence regarding the unique challenges associated with collecting PRO data from children, the evidence base for the reliability and validity of children's self-reported health assessments, and a synthesis of the future research that is needed to advance the field. The article is intended to address the use of pediatric PROs for medical product labeling, but this is a minor limitation in scope. Any clinical researcher who uses PROs in child and adolescent populations will find the work to be immensely helpful.

The ISPOR Task Force Report provided an overview of the self-report skills that are needed to respond to questionnaires. To reliably and validly complete health questionnaires, a respondent must be able to read questions (or comprehend questions read aloud), understand the meaning of health terms, and formulate responses that account for the recall period. We know remarkably little about the developmental trajectories of these skills. PRO researchers use cognitive interviewing methods to evaluate children's self-report capabilities. The validity of these methods for children, whose expressive language may lag their receptive language skills, however, is not well established; respondents who understand an item may be unable to verbalize reasons for their response choices. We also lack guidance on how many children of a particular age need to be interviewed to have sufficient information to ensure that when the items are used in the general population they will accurately assess the target health concepts. Research is needed, as Matza et al. [11] suggested, that develops and evaluates tools and methods for PRO completion skill screening. Such a skills assessment system would enable alteration of PRO mode of administration and perhaps scale content on the basis of an individual's cognitive skills rather than calendar age, moving the field (appropriately) away from age-based to stage-based PRO assessment.

Human development is a set of processes and mechanisms, rather than end states or skills. Development describes the pathways that result from individuals' dynamic and relational interactions with their environments, thereby leading to the formation of new capabilities and functional capacities. Importantly, human development transpires over the entire life course. It strikes me as odd that developmental considerations have been relegated to pediatric research. Cognitive skills may not develop in some adults, nearly one in four have low literacy, and in later years, skills may decline. We treat the age range 18 to 85 years as though it is a single, monolithic developmental stage of life. Adult PRO research could be strengthened by adding a developmental framework that not only addresses cognitive skills but

also accounts for whether health concepts are developmentally appropriate at each stage of life. Additional considerations that are important across the life course are the effects of changing biological, cultural, and contextual influences on the (developmentally appropriate) content of PRO scales. Developmental stage is also likely to be a strong determinant of individuals' preferences and priorities for treatment outcomes. In other words, the PRO concepts that are important to individuals may vary across the phases of the life course.

If we limit our view of pediatric PRO assessment to ages 0 to 17 years, then self-report, as the Task Force report indicates, can be justified for medical product labeling for only 10 of those 18 years (8–17 years of age). This leaves a large gap in our capacity to obtain children's perspectives on their health. Pediatric clinicians and parents know that children at young ages, even infants, can communicate feelings and sensations through nonverbal facial expressions and verbal utterances. As young children acquire language, we can obtain valuable information by directly interviewing them about their current health states. Creation of PROs for young children will require that we develop novel methods for observing their health and eliciting their verbalizations. Frequent momentary assessments (multiple times per day) [12] hold promise as a methodology that merits further investigation for young child PRO assessment.

Another aspect of children's development related to medical product labeling is concerned with the late effects of medical treatments. The developmental origins of chronic disease have been well established for a variety of chronic and mental health disorders [13,14]. Given the sensitivity of children's biology to environmental influences, it is plausible, and indeed likely, that medical products will have long-term effects on child health. Thus, we need to build data collection systems that evaluate pediatric PROs not only as immediate outcomes but also as outcomes that may not manifest themselves until long after exposure.

Numerous recruitment, ethical, and financial barriers to pediatric clinical research still need to be addressed if we are to secure the knowledge that children, families, and clinicians need to make evidence-based decisions about medical products. The pediatric research regulatory infrastructure in the United States reflects our society's impatience with the inadequacy of the medical product evidence base and continued reliance on off-label use of medical products among children. As the ISPOR Task Force Report on Pediatric PROs indicates, measurement of children's perspectives on their health has advanced sufficiently to merit the use of pediatric PROs in clinical research and for medical product claims. The scientific community has crossed the threshold from uncertainty regarding children's capacity to self-report about their health to an era when child self-reported health status instruments have been widely adopted by scientists and integrated into the research enterprise. These advances in pediatric PRO assessment are ensuring that children's voices will be part of the growing medical product evidence base.

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