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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

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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.

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Background to the Task Force

In March 2009, the ISPOR Health Science Policy Council recommended to the ISPOR Board of Directors that an ISPOR Good Research Practices Patient-Reported Outcomes (PRO) Task Force should be established to focus on the Assessment of Patient-Reported Outcomes in Children and Adolescents. The Board of Directors approved this PRO Task Force in March 2009. The Pediatric PRO Task Force chair (Dr. Matza) and co-chair (Dr. Patrick) chose task force members based on their experience in PRO assessment and research focusing specifically on children and adolescents. Members were selected to represent a diverse range of perspectives, including government (United States Food and Drug Administration), academia, research organizations, and the pharmaceutical industry. In addition, the task force had international representation with members from Germany, Spain, and the United States.

The Task Force initially met approximately every 2 months by teleconference to develop an outline and discuss issues to be included in the report. Face-to-face meetings were held in New Orleans in October 2009 and Atlanta in May 2010 to discuss these issues further and come to consensus on recommendations. In addition, the task force chair had a series of one-on-one teleconferences with members involved in drafting the manuscript. All task force members reviewed many drafts of the report and provided frequent feedback in both oral and written comments.

Preliminary findings and recommendations were presented in a forum at the ISPOR 15th Annual International Meeting in May 2010. Updated findings and recommendations were presented in a forum at the ISPOR 17th Annual International Meeting in June 2012. Comments received during these two forums were addressed in subsequent drafts of the report.

A draft of this report was distributed to the ISPOR PRO Review Group (which includes over 400 members) in March 2012. A revised draft was distributed to the entire ISPOR membership in January 2013. During these two rounds of review, over 250 written comments were received from 40 ISPOR members. Written comments were also provided by members of several regulatory and reimbursement agencies including three reviewers from the US Food and Drug Administration, one reviewer from Germany's Institute for Quality and Efficiency in Health Care (IQWiG), and one reviewer representing both the French National Authority for Health (Haute Autorité de Santé [HAS]) and the European Network for Health Technology Assessment (EUnetHTA).

All comments were considered, and most were substantive and constructive. The comments were discussed by the task force in a series of teleconferences and addressed as appropriate in revised drafts of the report. Once consensus was reached by all task force members, the final report was submitted to *Value in Health* in April 2013.

All written comments are published at the ISPOR Web site on the task force's Web page: http://www.ispor.org/TaskForces/PROChildrenAdolescents.asp. The task force report and Web page may also be accessed from the ISPOR homepage (www.ispor.org) via the purple Research Tools menu, Good Practices for Outcomes Research, heading: Patient Centered & Clinician Reported Outcomes Methods, and link: Assessment of PRO in Children and Adolescents. A list of reviewers is also available via the task force's Web page.

Introduction

A patient-reported outcome (PRO) instrument involves the report of health status coming directly from the patient without interpretation of the patient's response by a clinician, investigator, or anyone else [1,2]. Many aspects of medical conditions are known only by the patients themselves, and direct assessment of the patient perspective is necessary to thoroughly understand patients' experiences of disease and treatment. In recent years, there has been an increased emphasis on systematic development and validation of PRO instruments for use in clinical trials evaluating medical product efficacy. PRO instruments are often included in clinical trials with the intention of collecting data to support claims made about a medical product in the product label [3,4].

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have released guidelines for the assessment of PROs. The FDA guidance has had a strong influence on industry-funded PRO research since a draft was published in 2006 and finalized in 2009 [1]. This guidance provides an overview of PRO use in the context of medical product development, as well as guidance for developing and evaluating these instruments. A brief section of the guidance discusses PRO instruments intended for use with children and adolescents (Section III.G.1). This section begins by stating that "issues related to the development process for pediatric PRO instruments are similar to the issues detailed for adults." Then, the section continues by saying that the use of PRO instruments in pediatric populations introduces unique challenges that are not encountered in PRO research with adults. Several challenges are mentioned, including age-related vocabulary, comprehension of health concepts, the need to determine the lower age limit at which children can provide reliable and valid responses, and appropriate use of reports by informants other than the patients themselves. No specific recommendations, however, are provided for addressing these challenges.

Like the FDA, the EMA has provided recommendations for PRO measurement, particularly with regard to the assessment of health-related quality of life (HRQOL) [5]. The EMA guidance, however, does not discuss the use of PRO instruments with children and adolescents. In sum, there is limited available guidance for research involving pediatric PRO assessment related to medical product development.

Therefore, 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 in this report 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). The good research practices are summarized in Figure 1.

The challenges of choosing, developing, and implementing PRO instruments in children and adolescents have been reviewed and discussed in many previous publications [6–22]. Several published articles and book chapters have also provided lists and reviews of generic and condition-specific PRO instruments for children and adolescents [6,9,14,23–28]. The current task force report differs from this previous work because of its specific focus on pediatric PRO instruments in the context of medical product development and labeling.

The recommendations in this report are based on published research as much as possible. Pediatric PRO assessment, however, is a developing field of research, and empirical evidence is limited for some important areas of instrument design, development, validation, and implementation. Therefore, it is not currently possible to provide definitive recommendations for some of the issues discussed in the current report. In these situations, this task force report discusses the factors to consider when making decisions about the design and use of PRO instruments for children and adolescents. In addition, this report highlights areas in which further research is needed to advance the field of pediatric PRO assessment.