Themed Section: Evolution of EuroQoL

EQ-5D-Y as a Health-Related Quality of Life Instrument for Children and Adolescents: The Instrument's Characteristics, Development, Current Use, and Challenges of Developing Its Value Set

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A B S T R A C T

Objectives: Interest in the measurement of health-related quality of life (HRQoL) in children and adolescents has been increasing, and appropriate instruments are required for this target group. This article focuses on the EQ-5D-Y instrument, presenting an overview of its characteristics, development, and current use, and includes a discussion of methodological and conceptual issues related to the valuation of child health and the development of an EQ-5D-Y value set. **Methods:** This article brings together the experiences of the research team that developed and validated the EQ-5D-Y, supplemented by information derived from EQ-5D-Y study registrations on the EuroQol Group's website. **Results:** EQ-5D-Y is a child-specific and age-appropriate measure of HRQoL. Study registration data show that the instrument's use has steadily increased since its first publication. It has been used in various types of studies and in different disease areas. Currently there is no value set for EQ-5D-Y, and so its use in cost-utility analysis (CUA) is limited. There are methodological and

conceptual issues that affect the design of valuation studies for child health. Issues that are discussed include the need for separate value sets for children and adolescents, the choice of appropriate reference samples and valuation techniques, and the framing of the tasks. **Conclusions:** Research on EQ-5D-Y and its use has increased in the last years. Further research is required to clarify methodological issues regarding health state valuation in children and adolescents. This will support the development of a value set for EQ-5D-Y and the use of EQ-5D-Y in CUA.

Keywords: adolescents, children, EQ-5D-Y, health-related quality of life (HRQoL), valuation of health states

Background

The measurement of health-related quality of life (HRQoL) as an outcome parameter is of importance, not only in adults but also in children and adolescents. In observational or long-term studies, clinical trials, routine care studies, and population surveys, HRQoL instruments are used alongside traditional outcomes (eg, mortality, clinical parameters) to capture the burden of disease from the perspective of an individual. HRQoL measures developed for adults should not automatically be used to measure outcomes in children and adolescents because the issues and concepts for children may be different. HRQoL measures for children should

focus on how their illness affects their daily life and how they feel.[1-3] The design of HRQoL measures for children and adolescents should accommodate their developmental and cognitive abilities.[1,4]

The Mental Health Division of the World Health Organization (WHO) has published guidelines for the development of child-specific HRQoL instruments. These guidelines require the instruments to be child centered, age-appropriate, cross-culturally comparable, and essentially generic, with the possibility of the inclusion of disease-specific modules. Instrument development should incorporate the views of the target group.[5] The Food and Drug Administration (FDA) has also recommended

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age-appropriate wording and a short recall period or time frame to avoid comprehension and memory problems.[2,6,7]

Both of these guidelines and other literature recommend the use of self-report questionnaires in children and adolescents, if possible, and the avoidance of proxy reports.[5-8] In the past, self-report was deemed to be problematic because the reliability of children's judgments was questioned.[9,10] Nevertheless, proxy reports (eg, by parents) can also be biased, involving both underestimation and overestimation.[8,11,12] According to an ISPOR Task Force report, there is no single cutoff age enabling all children to reliably report their own health status.[4] Research on children's cognitive abilities has shown not only that children aged 8 years and above are able to answer and fill in age-appropriate questionnaires about their HRQoL,[4,13,14] but also that younger age groups might be able to give information about their health.[4] The reliability and validity of self-report measures improve with older children.[4] A parent proxy report probably provides the most appropriate way of measuring health in very young children.[15]

A variety of generic and disease-specific instruments measuring HRQoL of children and adolescents were developed either as single index or profile measures.[1,7] Few preference-based HRQoL measures designed for children and adolescents exist. This may limit the data available for cost-utility analysis (CUA) of interventions for children and adolescents.[1-3]

Over 10 years ago the EuroQol Group recognized that the EQ-5D-3L was not necessarily a suitable measure for use with children and adolescents and so established a research program to develop a child health measure. The group set out to adapt the original EQ-5D to make it appropriate for children, test the adaptations, and then generate value sets for this new measure. This process produced the EQ-5D-Y.[16] This article provides an overview of the current evidence regarding the EQ-5D-Y as a generic instrument that was specifically designed to measure HRQoL of children and adolescents. The characteristics of the instrument with respect to the descriptive system and the EQ-VAS are outlined. There is information on the pilot testing, and the measurement properties as well as on alternative versions. Applications of EQ-5D-Y based on studies registered on the EuroQol Group's website have been summarized. The article also describes the challenges in developing a value set for EQ-5D-Y so that health state utilities can be estimated for the measure. In this context, the research challenges associated with health state valuation for child and adolescent HRQoL instruments are tackled in some detail, followed by a short report of the valuation approaches employed by instruments other than EQ-5D-Y. The article finishes with some concluding remarks.

EQ-5D-Y

EQ-5D-Y is a generic, child-friendly self-complete instrument measuring HRQoL in children and adolescents aged 8 to 15 years. Its design is based on the EQ-5D-3L instrument, which was developed to measure HRQoL in adults. The EuroQol Group perceived a growing interest in measuring HRQoL in younger age groups and the need for a measure which would be appropriate and suitable to measure HRQoL in children and adolescents by self-report.[17] EQ-5D-Y was developed in 2009/2010 by a team of researchers from 7 countries.[16,18]

Descriptive System

The resulting descriptive system comprises 5 dimensions: mobility ("walking about"), self-care ("looking after myself"), usual activities ("doing usual activities"), pain or discomfort ("having pain or discomfort"), and anxiety or depression ("feeling worried, sad or unhappy"). The developmental process supported the applicability of the original EQ-5D-3L dimensions for children and adolescents. There was agreement that the 5 dimensions were also important for the HRQoL of children and adolescents. Nevertheless, some changes, especially in the wording of the dimensions, were made to clarify the meaning of the dimensions to younger respondents; for example, more appropriate examples for the dimension "usual activities" were chosen. The dimension "self-care" was renamed "looking after myself," and examples such as "washing and dressing" were included. "anxiety or depression" was replaced by "feeling worried, sad or unhappy."[16] Each dimension presents 3 levels of problems using the wording "no problems" (level 1), "some problems" (level 2), and "a lot of problems" (level 3).[17] The whole questionnaire refers to "your health TODAY."[17,19]

Like EQ-5D-3L, the descriptive system generates 243 different health states, which can be described by a 5-digit code, defined by a combination of one level for each of the 5 different dimensions (eg, 12132). Guidance of how to report and present EQ-5D-Y data can be found in the EQ-5D-Y user guide.[17]

EQ VAS

The respondent rates his or her overall health on the EQ VAS, a vertical scale from 0, labeled as "The worst health you can imagine," to 100, labeled as "The best health you can imagine."[16,17] In the development of the questionnaire, the EQ-5D-3L description of the VAS rating was changed to a child-friendly wording for the EQ-5D-Y.[16]

Overall, for the EQ-5D-Y, the 5 dimensions, the VAS wording, and the questionnaire layout were adapted to a more child-friendly format to ensure better comprehension.[16]

Pilot Testing of EQ-5D-Y and Comparison to EQ-5D-3L

The developed questionnaire was translated according to a standardized protocol into different languages (German, Italian, Spanish, and Swedish) and given to respondents aged 8 to 18. After self-completing EQ-5D-Y, the respondents participated in cognitive interviews designed to obtain information about comprehensibility, acceptability, and any misunderstandings related to the new instrument. Almost all children and adolescents answered the questions without any help, and comprehension was good. Only minor modifications to the other language versions were required, based on a number of specific cultural factors. For the English source version no further adaptations were needed.[16]

Subsequently, EQ-5D-3L and EQ-5D-Y were administered to a sample of school-aged children in Germany, Spain, and South Africa. Results obtained from the 2 versions were compared, and respondents indicated more problems on EQ-5D-Y for the dimensions "mobility," "having pain or discomfort," and "feeling worried, sad or unhappy." The EQ-5D-Y had fewer missing values and, overall, participants indicated that EQ-5D-Y was easier to understand than EQ-5D-3L.[16]

Feasibility, Validity, Reliability, and Sensitivity of EQ-5D-Y

Feasibility

Ravens-Sieberer et al. reported that completion data revealed only a small proportion of missing or inappropriate responses (between 0% and 2% in different countries). Their study showed that it was easy for the respondents to fill in the questionnaire.

Table 1 – Recommendations for use of youth and adult EQ-5D versions in different age ranges of children and adolescents.	
Age range	**Recommendation**
0-7 years	No self-reported EQ-5D-Y for youngest children available at present *For children aged 4-7 years one of the proxy versions can be used.*
8-11 years	Use EQ-5D-Y *The EQ-5D-Y is more understandable for children than the Adult EQ-5D.*
12-15 years	Both Youth and Adult EQ-5D versions can be used (overlapping area) *Generally, EQ-5D-Y is recommended. Nevertheless, depending on study design, the usage of the EQ-5D adult version might be possible.*
16 years and older	Use one of the Adult versions (EQ-5D-3L or EQ-5D-5L) *Possible exception: a study with only children up to 18 years—in this case EQ-5D-Y for older children would be recommended in order to have only one EQ-5D version in the study. The switchover to the adult version could bring discontinuity because the adult and child versions are two different instruments.*

Reference: EuroQol Group.[17]

Hence "the EQ-5D-Y is highly feasible for children as a HRQoL measure."[19] Feasibility was also shown in a population of young asthma patients and in children and adolescents with functional disabilities.[20,21]

Validity and Reliability

Convergent validity was supported by patterns of association with other child-specific HRQoL measures (eg, KIDSCREEN-27).[19] This was also observed in asthma patients.[20] In addition, EQ-5D-Y was used in comparison with the Child Health Utility 9D (CHU9D), another child-specific instrument. The results showed a high degree of agreement between these 2 instruments in measuring HRQoL and therefore pointed toward good convergent validity of EQ-5D-Y for application in adolescents.[22] EQ-5D-Y data showed fair to moderate levels of test–retest reliability (test–retest agreement of about 70%-99%).[19]

Sensitivity

The instrument's sensitivity and hence its ability to discriminate between small changes in HRQoL was reported to be limited, possibly owing to high ceiling effects.[19] The observation of ceiling effects in the adult version EQ-5D-3L was one reason for the development of EQ-5D-5L, which contains 5 levels in each dimension.[23] Currently, researchers are undertaking fundamental work to develop a version of the EQ-5D-Y with additional levels to improve its measurement properties.

EQ-5D-Y Versions and Their Usage

EQ-5D-Y has primarily been developed for use in children and adolescents aged 8 to 15 years. Table 1, however, presents more detailed recommendations on how to apply EQ-5D-Y for children and adolescents in different age ranges.[17]

The issue of proxy reports was considered at the beginning of the article in the context of WHO and FDA guidance. In addition to the self-complete questionnaire, 2 different proxy versions are available that have the same structure as EQ-5D-Y. Proxy versions can be completed (eg, by parents, relatives, or health care providers) when a child or an adolescent is not able to fill in EQ-5D-Y on his or her own. Proxy version 1 frame of reference is "the proxy rates how he/she rates the health of the child," and proxy version 2 indicates that "the proxy rates how he/she thinks the child would rate his/her own state if he/she were able to do so." The proxy versions (preferably version 1) can be applied to children aged 4 to 7 years and to children aged 8 years and older who are not able to fill in EQ-5D-Y themselves.[17]

Currently research is being undertaken concerning additional modules focusing on a special aspect or dimension in the form of a "bolt-on."[18] For EQ-5D-Y, a cognitive bolt-on has been developed and is now being tested in Germany.

The self-complete version of EQ-5D-Y is available in around 40 languages. In addition, the proxy versions are available in several languages. Versions for electronic data capture exist too.[17]

Interim Conclusion

In summary, EQ-5D-Y is a generic, self-complete health status instrument, which is designed to be child-specific and age-appropriate. It meets most of the WHO criteria outlined earlier because children and adolescents were involved in both steps of the development of EQ-5D-Y by way of interviews and a survey. EQ-5D-Y can measure HRQoL of children and adolescents in the given age range of 8 to 15 years. A possible advantage of the use of EQ-5D-Y in relation to EQ-5D-3L is that, given their similar structure, it may make it possible to measure HRQoL through childhood and into adulthood to measure changes over the course of a lifetime. This type of use of the measure requires further research.[19] A limitation to the applicability of EQ-5D-Y is that currently there is no value set available to determine a single index for the instrument to support use in economic evaluation. In the absence of a special value set for younger age groups, some researchers applied the adult value set in the context of children and adolescents.[24,25] Nevertheless, "it is not recommended to use the 3L value set as proxy value set for the EQ-5D-Y."[17] The EuroQol Research Foundation is currently working on research related to valuation in the EQ-5D-Y context.[17] The difficulties within this research field will be focused upon below.

EQ-5D-Y Application

Between November 2010 and March 2018, 586 studies using EQ-5D-Y were registered with the EuroQol Group. The use of the instrument is increasing year on year. In 2010-2011, on average, 2.5 EQ-5D-Y studies were registered per month, and by 2015 the average was 4.6. In 2018 the average number had reached 32.7 registered studies per month. EQ-5D-Y was used in different study designs, including interventional studies (200), observational research (185), routine data collection (51), and randomized controlled trials (RCT; 36). Most studies were conducted in the United Kingdom (155), followed by the United States (95), the Netherlands (36), and Sweden (29). The EQ-5D-Y has been applied in many different therapeutic areas, such as orthopedic conditions, diabetes, and other chronic conditions.

Research Challenges in Health State Valuation: In General and for EQ-5D-Y

There is a lack of child and adolescent HRQoL instruments that generate preference-based index values, thus limiting the use of CUA for health programs involving these age groups.[1-3] EQ-5D-Y is designed to address this gap, but the development of valuation studies of the EQ-5D-Y has been delayed because there is still no consensus about the valuation of health states for children and adolescents. Valuation studies are required to obtain people's preferences in terms of health, to produce a value set containing weights for different dimensions and levels of impairments. Value sets can then be used to calculate a preference-based utility index to be included in the calculation of quality-adjusted life years (QALYs), further enabling the use in CUA.[26] Many methodological and conceptual issues with respect to the design of these valuation studies are still unclear and controversial.[24,25,27] This section considers a number of important issues in the valuation of HRQoL in children and adolescents and relates these to EQ-5D-Y valuation: the need for separate value sets for children and adolescents; who should value health states of children and adolescents; the framing of the valuation task; and the feasibility of valuation techniques for children and adolescents asking them to value their own health states.

Separate Value Sets for Children and Adolescents?

Issues for general discussion

There is evidence to suggest that health state values for children or adolescents differ from values derived for adult health states. Busschbach et al. reported that being healthy in childhood was rated as twice as important as being healthy in the last decade of life.[28] Similar results were found referring to the relationship between age and the value of an increase in health.[29,30] Thorrington and Eames concluded that adults and children and adolescents perceived and valued health differently, and therefore "the assumption that adult-specific health utilities are valid in adolescents or young children is potentially misleading."[25] In addition, Petrou found substantial evidence that greater weight was placed upon health gains by children and adolescents than on health gains by adults.[27] Thus, considering these results, it might be assumed that separate child-specific values sets are necessary in the calculation of a preference-based HRQoL index for children and adolescents.[31]

Specific issues to EQ-5D-Y

Two recent studies examined the differences in valuing the same health states for children and adults, where health states were based on the dimensions and levels of EQ-5D-Y. First, using the VAS valuation technique, Kind et al. showed that adults gave lower values for children's health states than they gave for themselves or for other adults.[32] Second, Kreimeier et al. used forms of time trade-off (TTO) and discrete choice experiments (DCE).[33] In the conventional TTO approach, respondents compare a life in an impaired health state for 10 years to a life in full health but with a shorter duration. Using an iteration process, the respondent is asked about the number of life years remaining at full health at which he or she is indifferent toward either living for a longer time in impaired health or living for a shorter time but in full health.[34,35] In a DCE, respondents are asked to think about 2 different health states and to choose the better one of the two.[36] This study by Kreimeier et al. reported higher mean TTO values for the child perspective than for the adult perspective. It might be assumed that the inclusion of shortened lives in the c-TTO tasks might have led a stronger preference for longer lives when adults completed the tasks for children. That resulted in higher values for child health states relative to adult health states.[33] Because both studies[32,33] showed differences in values given for child and adult health states, they support the argument that separate EQ-5D-Y value sets for children and adolescents might be necessary.[32,33]

Who Should Value Health States of Children and Adolescents?

Issues for general discussion

If separate value sets are needed, then the question who should value health states of children and adolescents arises. Published research has considered the role of different groups for providing preference weights for a child measure. These include the general population, patients, or relatives, such as parents.[19,24,37,38]

The general population. There is a normative argument that the preferences of the general population should be the most relevant for guiding resource allocation decisions (compared with patients).[19,37,38] CUA is often used to inform policy decisions, and thus a societal viewpoint (regarding HRQoL) should be derived from representatives of the general population.[37,38] The tax-paying general population pays for health care interventions in children and adolescents, and so this population might be appropriate in eliciting preferences for children's health states.[26,37] The main argument against this approach is that these people may not have enough information about the health states being valued because most respondents have never experienced these particular health states.[26,38,39]

If the general population is asked to value health states of children and adolescents, it is adults who make judgments about the severity of health problems of younger age groups. As noted earlier, adults might feel differently about health problems owing to their experiences in life and they might give different weights to different impairments compared with younger people. There is evidence that adults' preferences differ from adolescents' preferences when identical health states are valued.[40,41]

Patients. It has been advocated that patients should be asked for their preference values because they have experienced health impairments.[26,38] Nevertheless, this approach has been criticized in that patients might have an incentive to overestimate the burden caused by their health impairments so that their disease receives greater consideration with respect to resource allocation.[26,37,38] Contrarily, patients might become accustomed to their health problems, for example, by coping strategies or adaptation. Hence, they might rate health problems less severe than the general population.[26] There is evidence that valuing real or experienced health states (by asking patients) differs from valuing hypothetical health states when taking an ex ante perspective (ie, asking the general population) because people have difficulties in predicting future preferences.[37]

Parents. Relatives could also be asked to rate health states as they are close to the patients and thus able to estimate the influence of health impairments.[42] In the context of children and adolescents, in particular, it is argued that parents are the appropriate respondents for health state valuation. They know their children and to some degree experience how health problems influence their lives.[24,43] Their reports better match with children's reports than those of health care providers or persons from the general population who do not have children.[24,44] Nevertheless, it might be problematic if parents are not able to differentiate between the effects health problems have on the child and the spillover effects the child's health problems have on themselves, relatives, or other children.[45] Hence, whether parents can give reliable values for the health states of children

and adolescents and whether they are the right valuation sample to choose remain unresolved.

Specific issues to EQ-5D-Y

Previous research has estimated EQ-5D-Y value sets based on the adult general population. This choice is related to a societal perspective, where a representative sample of the general population is asked to value the health states, as is the case for the EuroQol adult instruments.[46] Craig et al. developed an experimental value set for EQ-5D-Y asking adults by using an unconventional approach, a "series of non-adaptive paired comparisons," including the choice between a loss of HRQoL for a child and a loss in lifespan.[47] In another study, Kreimeier et al. asked the adult general population to value health states of children and adolescents by using c-TTO and DCE.[33]

Framing of the Valuation Task

Issues for general discussion

If adults value health states of children and adolescents, the framing of the preference task needs to be considered carefully. This includes the wording employed and, more specifically, the perspective being adopted in the preference elicitation exercise. The perspective taken could result in different preferences. Preferences appear to be different if a person is asked to value health states for him or herself or for another adult person. As noted earlier, there can be differences in values given for health states of children and adolescents and those given for adult health states.[29,30,32,40,47] Also, preferences might be different if persons are asked to consider a perspective such as "think of a child" or "think, you are a child." Further, the given age of a child might influence the result of the valuation task. People might give different values when asked to consider an "8-year-old child" or a "15-year-old adolescent." Craig et al., for example, showed that greater value was placed on HRQoL losses at age 7 than at age 10 when adults valued the health states of children.[47] Also, different values might be elicited when a person is asked to value a health state of "a hypothetical child" or "the own child" or "a child you know."

These framing issues constitute a major difference compared with the valuation task conducted in the context of preference-based HRQoL value sets in adults. Usually, adults are asked to imagine themselves being in the health states when completing the task, as opposed to someone else being in the health state as is done when adults are asked to imagine a child living in a health state.[47]

Specific issues to EQ-5D-Y

Initial approaches to the valuation of EQ-5D-Y health states framed the tasks by asking the respondents to "think of a 10-year-old child."[32,36] So, the respondent is asked about a hypothetical child. The specific age was chosen to make it easier for the respondents to imagine a child in the age range for which EQ-5D-Y is recommended. If an age range or no age were given at all, a researcher would not know what kind of child the respondent is thinking about.

Feasibility of Valuation Techniques for Children and Adolescents Valuing Their Own Health States

Issues for general discussion

In contrast to the approach of asking adults to value child health states, the approach that considers the point of view of children and adolescents themselves within the health state valuation process is increasingly discussed and is being employed in the context of another child-specific instrument.[41,48-51] This brings up the challenge of choosing a preference elicitation technique that can be used in this younger population. There are doubts about the cognitive ability of children and adolescents to value health states and whether they are able to contemplate their whole lifespan.[24,25,47] The conventional valuation techniques such as TTO and standard gamble (SG) "place a considerable cognitive burden on respondents who are required to evaluate a series of separate health states successively until the point of indifference is found."[48] Furthermore, the SG often requires respondents to think about immediate death. This is considered ethically inappropriate for children and adolescents because it may be too upsetting.[48] In recent years, DCE has been increasingly used. This valuation method is considered easier to understand for respondents in vulnerable populations such as younger age groups. Nevertheless, there are methodological limitations with respect to QALY estimation if this approach is used.[50]

Within the valuation debate, the split between younger children and adolescents has also been discussed, given that the whole group is very heterogeneous. Although adolescents might be able to value health states using one of the conventional valuation techniques, younger children may not be able to apply these techniques and thus proxy respondents for the valuation of children's health states may be required.[45] An argument that could be stated against asking children and adolescents themselves is that they do not belong to the tax-paying population. Thus, they should not be able to influence the allocation of resources through their health state preferences.[26,37,38]

Valuation Approaches of Other Child-Friendly Utility Instruments

The issues of health state valuation in children and adolescents are not only a concern of the EQ-5D-Y instrument. Other child-specific instruments have faced the same challenges. According to Chen and Ratcliffe, currently there are 9 generic preference-based multi-attribute utility measures used within pediatric populations.[52] Nevertheless, the list of instruments should be treated with caution. Based on a narrow definition, to date, only 3 generic preference-based HRQoL instruments specifically developed for application in the younger age group are available. The 16D/17D, HUI2/HUI3, and CHU9D provide value sets to generate a single HRQoL index for children and adolescents.[50,52] These instruments employ different approaches in the context of health state valuation. The 16D and 17D and the HUI2 and HUI3 use only traditional valuation techniques such as rating scale or SG and ask only adults to value child health states.[53-57] For the CHU9D the research team also considered more innovative approaches to the valuation of the health states of children and adolescents using the DCE method and asking adults, but also children and adolescents, to value the health states.[41,48,49,51,58]

Conclusions

The amount of research on HRQoL in younger age groups has increased within the last 2 decades and research with respect to health state valuation in children and adolescents has also been initiated. This article has reviewed the outcomes of this research with specific reference to the development and construction of the EuroQol Group's instrument, the EQ-5D-Y. Issues in the measurement and valuation of HRQoL have been examined. The child-friendly generic EQ-5D-Y has been shown to be feasible in assessing HRQoL in the age group 8 to 15. Nevertheless, it lacks a value set, which limits its use as a generic preference-based single index measure of benefit for use in CUA.

It could be argued that more complicated conceptual and methodological challenges surround this research field in the

younger population compared with research in adults. To enable appropriate economic evaluation of health care interventions for children and adolescents, further research is required to clarify questions raised concerning who should value health states of children and adolescents, the appropriate framing and perspective of these tasks, and which valuation technique is feasible. The experience in adult valuation studies is helping researchers in developing a preference-based value set for the EQ-5D-Y. This can be expected to increase the use of EQ-5D-Y and make CUA in pediatric areas more tractable.

Acknowledgment

R E F E R E N C E S

1. Solans M, Pane S, Estrada M-D, et al. Health-related quality of life measurement in children and adolescents: a systematic review of generic and disease-specific instruments. Value Health 2008;11(4):742–64.
2. Ravens-Sieberer U, Erhart M, Wille N, et al. Generic health-related quality-of-life assessment in children and adolescents: methodological considerations. Pharmacoeconomics 2006;24(12):1199–220.
3. Bullinger M, Schmidt S, Petersen C. Assessing quality of life of children with chronic health conditions and disabilities: a European approach. Int J Rehabil Res 2002;25(3):197–206.
4. 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 2013;16(4):461–79.
5. Division of Mental Health, World Health Organization (WHO). Measurement of Quality of Life in children: Report of a WHO/IACAPAP Working Party. http://www.who.int/mental_health/media/en/663.pdf. Accessed May 6, 2018.
6. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf. Accessed May 9, 2018.
7. Matza LS, Swensen AR, Flood EM, Secnik K, Leidy NK. Assessment of health-related quality of life in children: a review of conceptual, methodological, and regulatory issues. Value Health 2004;7(1):79–92.
8. Ellert U, Ravens-Sieberer U, Erhart M, Kurth B-M. Determinants of agreement between self-reported and parent-assessed quality of life for children in Germany-results of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). Health Qual Life Outcomes 2011;9:102.
9. Levi R, Drotar D. Critical issues and needs in health-related quality of life assessment of children and adolescents with chronic health conditions. In: Drotar D, editor. Measuring Health-Related Quality of Life in Children and Adolescents: Implications for Research and Practice. Mahwah, NJ: Erlbaum; 1998, pp. 3–25.
10. Eiser C, Jenney ME. Measuring symptomatic benefit and quality of life in paediatric oncology. Br J Cancer 1996;73(11):1313–6.
11. Khoshkhui M, Jafari P, Afrasiabi M, Orooj M, Kashef S. Level of agreement between children with asthma and their parents on quality of life. Iran J Med Sci 2016;41(2):86–93.
12. Russell KMW, Hudson M, Long A, Phipps S. Assessment of health-related quality of life in children with cancer: consistency and agreement between parent and child reports. Cancer 2006;106(10):2267–74.
13. Rebok G, Riley A, Forrest C, et al. Elementary school-aged children's reports of their health: a cognitive interviewing study. Qual Life Res 2001;10(1):59–70.
14. Riley AW. Evidence that school-age children can self-report on their health. Ambul Pediatr 2004;4(4):371–6.
15. Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. Qual Life Res 2001;10(4):347–57.
16. Wille N, Badia X, Bonsel G, et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. Qual Life Res 2010;19(6):875–86.
17. EuroQol Group. EQ-5D-Y User Guide.: Basic information on how to use the EQ-5D-Y instrument. http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/EQ-5D-Y_User_Guide_v1.0_2014.pdf. Accessed May 10, 2018.
18. Brooks R. The EuroQol Group After 25 Years. Dordrecht: Springer; 2013.
19. Ravens-Sieberer U, Wille N, Badia X, et al. Feasibility, reliability, and validity of the EQ-5D-Y: results from a multinational study. Qual Life Res 2010;19(6):887–97.
20. Bergfors S, Åström M, Burström K, Egmar A-C. Measuring health-related quality of life with the EQ-5D-Y instrument in children and adolescents with asthma. Acta Paediatr 2015;104(2):167–73.
21. Burström K, Bartonek Å, Broström EW, Sun S, Egmar A-C. EQ-5D-Y as a health-related quality of life measure in children and adolescents with functional disability in Sweden: testing feasibility and validity. Acta Paediatr 2014;103(4):426–35.
22. Chen G, Flynn T, Stevens K, et al. Assessing the health-related quality of life of Australian adolescents: an empirical comparison of the child health utility 9D and EQ-5D-Y instruments. Value Health 2015;18(4):432–8.
23. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20(10):1727–36.
24. Noyes J, Edwards RT. EQ-5D for the assessment of health-related quality of life and resource allocation in children: a systematic methodological review. Value Health 2011;14(8):1117–29.
25. Thorrington D, Eames K. Measuring health utilities in children and adolescents: a systematic review of the literature. PLoS One 2015;10(8):e0135672.
26. Brazier J. Measuring and Valuing Health Benefits for Economic Evaluation. New York: Oxford University Press; 2009.
27. Petrou S. Should health gains by children be given the same value as health gains by adults in an economic evaluation framework. In: Ungar WJ, editor. Economic Evaluation in Child Health. Oxford: Oxford University Press; 2010, 271–288.
28. Busschbach JJ, Hessing DJ, de Charro FT. The utility of health at different stages in life: a quantitative approach. Soc Sci Med 1993;37(2):153–8.
29. Tsuchiya A. Age-related preferences and age weighting health benefits. Soc Sci Med 1999;48(2):267–76.
30. Tsuchiya A. The Value of Health at Different Ages. http://www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20184.pdf. Accessed May 6, 2018.
31. Jelsma J, McKenzie J, Rama L. Differences in subjective construction of Health Related Quality of Life (as described by the components of the EQ-5D) for adults and children. Oxford, United Kingdom: 28th Scientific Plenary Meeting of the EuroQol Group, 2011; 2012.
32. Kind P, Klose K, Gusi N, Olivares PR, Greiner W. Can adult weights be used to value child health states? Testing the influence of perspective in valuing EQ-5D-Y. Qual Life Res 2015;24(10):2519–39.
33. Kreimeier S, Oppe M, Ramos-Goñi JM, et al. Valuation of EuroQol Five-Dimensional Questionnaire, Youth Version (EQ-5D-Y) and EuroQol Five-Dimensional Questionnaire, Three-Level Version (EQ-5D-3L) Health States: the impact of wording and perspective. Value Health 2018. https://doi.org/10.1016/j.jval.2018.05.002.
34. Attema AE, Edelaar-Peeters Y, Versteegh MM, Stolk EA. Time trade-off: one methodology, different methods. Eur J Health Econ 2013;14(Suppl 1):53–64.
35. Oppe M, Devlin NJ, van Hout B, Krabbe PFM, Charro F de. A program of methodological research to arrive at the new international EQ-5D-5L valuation protocol. Value Health 2014;17(4):445–53.
36. Stolk EA, Oppe M, Scalone L, Krabbe PFM. Discrete choice modeling for the quantification of health states: the case of the EQ-5D. Value Health 2010;13(8):1005–13.
37. Brazier J, Akehurst R, Brennan A, et al. Should patients have a greater role in valuing health states? Appl Health Econ Health Policy 2005;4(4):201–8.
38. Torrance GW. Measurement of health state utilities for economic appraisal. J Health Econ 1986;5(1):1–30.
39. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. Br Med Bull 2010;96:5–21.
40. Ratcliffe J, Stevens K, Flynn T, Brazier J, Sawyer MG. Whose values in health? An empirical comparison of the application of adolescent and adult values for the CHU-9D and AQOL-6D in the Australian adolescent general population. Value Health 2012;15(5):730–6.
41. Ratcliffe J, Huynh E, Stevens K, et al. Nothing about us without us? A comparison of adolescent and adult health-state values for the Child Health Utility-9D using profile case best-worst scaling. Health Econ 2016;25(4):486–96.
42. Schöffski O. Nutzentheoretische lebensqualitätsmessung. In: Schöffski O, editor. Gesundheitsökonomische Evaluationen. Berlin: Springer; 2008.

43. Ungar WJ. Challenges in health state valuation in paediatric economic evaluation: are QALYs contraindicated? Pharmacoeconomics 2011;29(8):641−52.
44. Theunissen NCM, Kamp GA, Koopman HM, et al. Quality of life and self-esteem in children treated for idiopathic short stature. J Pediatr 2002;140(5):507−15.
45. Prosser LA, Hammitt JK, Keren R. Measuring health preferences for use in cost-utility and cost-benefit analyses of interventions in children: theoretical and methodological considerations. Pharmacoeconomics 2007;25(9):713−26.
46. EuroQol Group. EQ-5D-3L User Guide: Basic Information on How to Use the EQ-5D-3L Instrument. https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-3L_UserGuide_2015.pdf. Accessed April 5, 2018.
47. Craig BM, Greiner W, Brown DS, Reeve BB. Valuation of child health-related quality of life in the United States. Health Econ 2016;25(6):768−77.
48. Ratcliffe J, Flynn T, Terlich F, et al. Developing adolescent-specific health state values for economic evaluation: an application of profile case best-worst scaling to the Child Health Utility 9D. Pharmacoeconomics 2012;30(8):713−27.
49. Ratcliffe J, Chen G, Stevens K, et al. Valuing Child Health Utility 9D health states with young adults: insights from a time trade off study. Appl Health Econ Health Policy 2015;13(5):485−92.
50. Ratcliffe J, Couzner L, Flynn T, et al. Valuing Child Health Utility 9D health states with a young adolescent sample: a feasibility study to compare best-worst scaling discrete-choice experiment, standard gamble and time trade-off methods. Appl Health Econ Health Policy 2011;9(1):15−27.
51. Ratcliffe J, Huynh E, Chen G, et al. Valuing the Child Health Utility 9D: using profile case best worst scaling methods to develop a new adolescent specific scoring algorithm. Soc Sci Med 2016;157:48−59.
52. Chen G, Ratcliffe J. A review of the development and application of generic multi-attribute utility instruments for paediatric populations. Pharmacoeconomics 2015;33(10):1013−28.
53. McCabe C, Stevens K, Roberts J, Brazier JE. Health State Values for the HUI 2 descriptive system: results from a UK survey. http://eprints.whiterose.ac.uk/42970/1/HEDS_DP_03-03.pdf. Accessed November 17, 2015.
54. Torrance GW, Feeny DH, Furlong WJ, et al. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. Med Care 1996;34(7):702−22.
55. Feeny D, Furlong W, Barr RD, et al. A comprehensive multiattribute system for classifying the health status of survivors of childhood cancer. J Clin Oncol 1992;10(6):923−8.
56. Apajasalo M, Sintonen H, Holmberg C, et al. Quality of life in early adolescence: a sixteen-dimensional health-related measure (16D). Qual Life Res 1996;5(2):205−11.
57. Apajasalo M, Rautonen J, Holmberg C, et al. Quality of life in pre-adolescence: a 17-dimensional health-related measure (17D). Qual Life Res 1996;5(6):532−8.
58. Stevens K. Valuation of the Child Health Utility 9D Index. Pharmacoeconomics 2012;30(8):729−47.