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Assessment of Health-Related Quality of Life in Children: A Review of Conceptual, Methodological, and Regulatory Issues

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ABSTRACT

Recently, the FDA has encouraged testing of medications among pediatric patients during drug development. Pharmaceutical companies have responded by conducting more clinical trials among children, and researchers are becoming aware of the unique challenges of assessing pediatric health outcomes, including health-related quality of life (HRQL). Like adults, children experience effects of illness and treatment beyond physiologic outcomes. Further pediatric HRQL research is necessary to examine these broader psychosocial outcomes and provide a thorough understanding of the effects of treatment on children's health status. The purpose of the current review is to discuss key regulatory and methodologic developments and provide guidance for future research on pediatric HRQL. This review of pediatric HRQL assessment includes five sections: 1) recent pediatric regulatory developments in the United States; 2) issues in defining and conceptualizing pediatric HRQL, including the importance of contextual variables such as family and peer systems; 3) methodologic issues (e.g., the proxy question, developmental differences, response sets) with recommendations for addressing these issues in clinical trials; 4) validated generic and condition-specific pediatric HRQL measures; and 5) a recommendation for additional research on the HRQL impact of childhood psychiatric disorders. It is advocated that assessment of HRQL among children should be conducted regularly as an integral part of drug development.

Keywords: health-related quality of life, quality of life, pediatric, children, regulatory, assessment.

Introduction

Historically, drug testing has not frequently been conducted among pediatric samples, possibly because of the added complexities of engaging children as subjects in medical research. Without controlled pediatric clinical trials, physicians and parents have remained uncertain about many drug treatment outcomes in this population. Thus, the FDA has recently issued a series of regulations to encourage pediatric drug testing as an integral part of drug development.

Pharmaceutical companies have responded to these regulations by conducting more clinical trials with pediatric samples. These pediatric trials have focused primarily on efficacy and safety end points, whereas relatively little research has examined the impact of drug treatment on children's health-related quality of life (HRQL). Like adults, children experience impacts of illness and treatment beyond the purely medical effects. More research on HRQL among children is necessary to identify these broader outcomes and provide a thorough understanding of children's health status. Consequently, a small but growing body of research has examined pediatric HRQL, and researchers are becoming more aware of the unique challenges involved in assessing HRQL among children.

The purpose of the current review is to discuss key regulatory and methodological developments and provide guidance for future research on pediatric HRQL. This review includes five sections: 1) recent pediatric regulatory developments in the United States; 2) definition and conceptualization of pediatric HRQL; 3) methodologic issues relating to the measurement of pediatric HRQL with recommendations for addressing these issues in clinical trials; 4) generic and condition-specific measures of pediatric HRQL; and 5) a recommendation for future research on the HRQL impact of psychiatric disorders in children.

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Review of Pediatric-Specific Regulatory Developments in the United States

In recent years, several regulations have been introduced with the intent to encourage pharmaceutical companies to conduct pediatric clinical trials. The Pediatric Exclusivity Provision, which was part of the FDA Modernization Act (FDAMA) of 1997, provided a significant financial incentive for pharmaceutical companies who conducted drug testing among children [1,2]. This provision required the Food and Drug Administration (FDA) to create and annually update a list of drugs for which additional pediatric research may lead to improved treatment outcomes for children. The FDA requests pediatric studies for drugs on this list, and if a pharmaceutical company responds by conducting a study according to acceptable scientific standards, then the company is given 6 additional months of market exclusivity for this drug. The FDA can also request pediatric studies for drugs that are not on the priority list, and pharmaceutical companies are permitted to ask the FDA to issue a written request for a study proposal. The Exclusivity Provision, which was originally intended to apply for only 5 years beginning in 1997, was extended for an additional 5 years by the Senate and House of Representatives as part of the Best Pharmaceuticals for Children Act.

The Pediatric Rule [3] followed the FDAMA of 1997. This gave the FDA the authority to compel companies to conduct pediatric research for new and marketed drugs and biologic products that are intended for children. Specifically, the rule required that studies be conducted: 1) for drugs used to treat substantial numbers of children; 2) for drugs that could offer therapeutic benefits to children; and 3) if the absence of adequate testing and labeling for children could pose significant risk [1,2]. In 2000, the updated FDA Pediatric Rule required manufacturers to include pediatric data in applications for new drugs as well as applications to extend indications for drugs expected to be used substantially in children, defined as at least 50,000 uses of the drug in the entire pediatric population [2]. The Pediatric Rule was temporarily suspended in March 2002, before being reinstated 1 month later [4,5].

The dramatic increase in pediatric drug testing since 1997 suggests that these regulations have been successful. Prior to the Exclusivity Provision and the Pediatric Rule, the FDA requested few pediatric studies, and pharmaceutical companies completed even fewer. Drug companies promised to conduct 71 postmarketing pediatric clinical trials between 1991 and 1996, but only 11 were completed [6]. As of April 2002, however, pharmaceutical companies had submitted 303 proposed study requests, the FDA had issued 237 written requests, and 54 drugs had received the 6-month exclusivity extension [7,8].

Conceptualizing Pediatric Health-Related Quality of Life

Defining Pediatric HRQL

Definitions of HRQL vary widely, but there are two central aspects of this construct that are inherent in most definitions [9–11]. First, HRQL is subjective, and therefore, it should be assessed from the patient's perspective whenever possible. Second, HRQL is a multidimensional construct that integrates a broad range of outcomes. One definition from the adult health outcomes literature that includes both of these components describes HRQL as an individual's subjective perception of the impact of health status, including disease and treatment, on physical, psychologic, and social functioning [12]. Although this general definition also applies to HRQL of children, the specific aspects of a child's life that comprise these three domains of functioning are different. Thus, when designing a pediatric HRQL instrument, it is important to ensure that items correspond to experiences, activities, and contexts that are directly relevant to the age of the sample.

The Central Role of Context in Child Development and Pediatric HRQL

When assessing children's social and psychological functioning, it is particularly important to remember that children are embedded within multiple social contexts including the family, the child's peer group, the classroom, and the community [13]. Each of these contexts is likely to contribute to HRQL and mediate the impact of disease and treatment on the child. For example, asthma is a disease that has been shown to impair HRQL in adults and children [14], but the specific effects of asthma are likely to be different for children because of their context. Asthma could limit a child's participation in play and athletics with peers, leading to social and emotional consequences that are different from those experienced by adults with the same disease. Thus, instruments designed to assess HRQL among children with asthma must assess child functioning within the relevant contexts. One such instrument is the Pediatric Asthma Quality of Life Questionnaire, which refers to typical child contexts such as

playing at recess, playing with friends, and riding a bicycle [15].

Developmental theorists have often asserted that the relationship between children and their social context is complex, involving simultaneous mutual influence among children and multiple contexts [13,16]. According to this theoretical perspective, children are active agents exerting an influence upon their context while simultaneously being shaped by their context. This bidirectional influence has been demonstrated by empirical research on parent–child interaction, in which children and parents have been observed to mutually influence each other's behavior [17,18]. Furthermore, children's functioning and behavior within their multiple social contexts are linked. For example, children's experiences within the family have been shown to contribute to their behavior, social cognition, friendship patterns, and level of acceptance from peers [19–22]. Researchers have suggested that characteristics of these contextual factors, such as families, peer relationships, local health clinics, and neighborhoods, should be included in assessment and analysis of pediatric health outcomes and quality of life [23,24].

There are two reasons that context is qualitatively different for children than for adults. First, contextual factors have been shown to have a long-term influence on children's social and psychologic development. For example, peer rejection in childhood is associated with numerous long-term negative outcomes including delinquency and school dropout [25]. Second, children have less power than adults to make significant changes to their context. Adults who have adequate financial resources or social support can leave a problematic workplace or a dysfunctional marriage. In contrast, children typically do not have the option of significantly changing a problematic environment.

In sum, context plays a different and possibly more important role for children than for adults, and children's quality of life depends on complex interactions between the child and multiple social contexts. Assessment of pediatric HRQL must consider these contextual variables such as family functioning, relationships with peers, and community factors. Furthermore, because the impact of disease and treatment may be substantially different for adults and children, HRQL outcomes from clinical trials with adults cannot be applied to children. It is therefore necessary to directly examine HRQL among children, rather than estimating pediatric HRQL outcomes based on research with adult samples.

Why Pediatric HRQL Research Is Necessary

Although pediatric clinical trials focus primarily on efficacy and safety, there is growing consensus that assessment of HRQL outcomes is also necessary to provide a complete picture of children's health status [11,26,27]. Conceptually, HRQL instruments are designed to assess a broader range of children's day-to-day functioning than clinical measures, and empirical findings suggest that HRQL measures provide unique information beyond clinical symptoms. For example, HRQL has been shown to be only moderately correlated with measures of symptom severity in studies of pediatric asthma [14,15], indicating that HRQL and clinical symptoms are related, but distinct from each other. Thus, HRQL instruments can be included in clinical trials as a complement to the traditional clinical measures of efficacy and safety. In combination, HRQL and clinical measures can provide a complete assessment of the impact of disease and treatment on children's overall well-being. Research that incorporates this comprehensive perspective can be used to inform pediatric health policy, treatment guidelines, and treatment of individual children.

Methodological Issues in Pediatric HRQL Assessment

This section reviews five methodological issues that must be considered when designing a measure or a study of pediatric HRQL. In each of the five areas, relevant empirical research is discussed, and practical recommendations are offered.

The Youngest Age at Which Children Can Report their HRQL

Researchers have made recommendations regarding the youngest age at which children can reliably report their health status and HRQL. Opinions vary, but it is generally estimated that children can begin reporting the more concrete domains of their own HRQL between 4 and 6 years old [14,28,29]. Self-report HRQL instruments have been designed and psychometrically validated for children in this young age range, including the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ; ages 6–12) [30] and the Childhood Asthma Questionnaire—Form A (CAQA; ages 4–7) [31].

Prior research has identified several characteristics that should be considered when determining the lower age cutoffs for a questionnaire assessing HRQL. In a review of pediatric health outcomes literature, Landgraf and Abetz [32] indicated that

there are age-related differences in the type of health concepts that children can comprehend. They report that children as young as age 5 can provide empirically reliable reports on concrete health concepts such as pain and medication use. In contrast, questionnaires that assess relatively subjective or abstract domains of HRQL, such as the emotional impact of illness, will likely be appropriate for older children.

The level of language comprehension may also place a lower limit on the age appropriateness of a questionnaire. A study that assessed children's understanding of health-related terms found that only 57% of 5-year-old children had a good understanding of the word "nervous" [33]. By age 8, all children in the sample understood this term (see Fig. 1) [33]. When designing self-administered paper-and-pencil questionnaires, it is also essential to consider the typical reading levels of children in the intended age range [32–34].

In sum, children as young as age 4 can often provide some information on concrete aspects of their health status. Assessment of more subjective HRQL domains may require a somewhat older sample. The reliability and validity of data provided by children depends on the complexity of the constructs and terminology used. The lower age limit will also vary according to individual differences in children's cognitive skills and their understanding of health status.

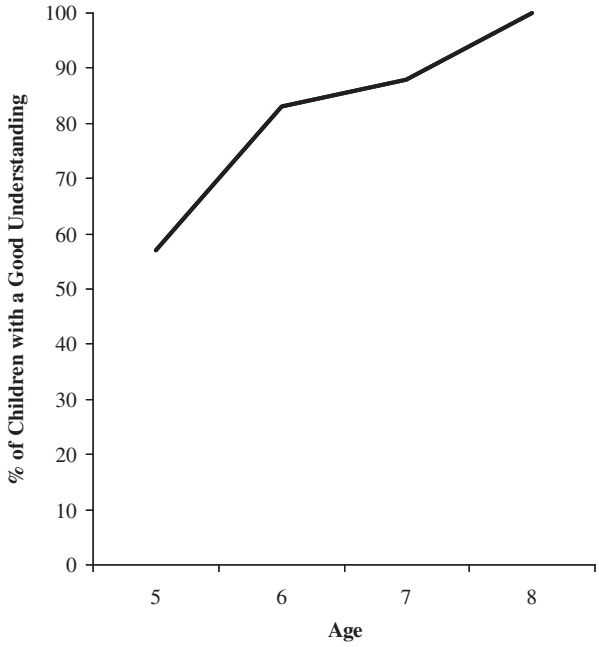


Figure 1 Age-related differences in children's understanding of the term "nervous" [33].

There are several ways to address this issue when assessing health status and HRQL in pediatric clinical trials. First, when developing a questionnaire, it is necessary to conduct pilot testing and careful cognitive debriefing with children of different ages in order to determine the lower age limit at which children can understand the questions and provide reliable and valid responses. Second, when determining the lower age limit of a clinical trial sample, it will be necessary to consider the disease area, the anticipated effects of the drug being tested, and the type of domains to be assessed. If the primary interest is in the drug's impact on physical domains, the trial can include self-report instruments designed for younger children. If the drug is expected to improve psychological or social domains of HRQL, it will be necessary to assess older children or use proxy reporters for younger children (see discussion of proxy issue later in this article). Third, because greater variability is expected with younger children due to measurement error, a larger sample size will be required to detect treatment effects.

The Proxy Question

There is substantial debate in the pediatric health outcomes literature concerning who is the most appropriate respondent when assessing children's HRQL [27]. Some researchers advocate questioning the child directly, whereas others prefer to use a parent or primary caregiver as a proxy respondent. Studies have examined this question by assessing the degree of agreement between parent and child report. The guiding assumption of these studies is that a high level of agreement would indicate that either the child or the parent could be used as the respondent without compromising validity of the HRQL assessment. In the case of disagreement, however, researchers would need to determine whose report is more reliable or appropriate for subsequent studies.

Empirical investigations of agreement between parent and child report of the child's health status and HRQL have yielded mixed results. Some studies report high parent–child agreement [32], whereas others have found low agreement [35]. The degree of agreement may depend on several factors, including the domain that is assessed. For example, correlations between parent and child report have been shown to be higher for observable physical domains than nonobservable emotional domains [27]. Studies that have considered the child's age have not reported consistent results. Some studies have found that older age was associated with greater parent–child agreement [36], whereas other

investigations have reported either the opposite [37] or no significant age effects [27]. Similarly, research examining the impact of the child's health on parent–child agreement has yielded conflicting information. Several studies have found greater parent–child agreement for sick children [27], whereas others have found greater agreement between parents and healthy children [38]. One study reported that children provide lower estimates of HRQL than their parents [39], but this has not been consistently replicated [27]. In sum, agreement between parent and child report of HRQL varies considerably, and further research is needed to clarify the factors that may influence this level of agreement.

Given these conflicting results, it is not yet possible to provide an empirically based, conclusive answer to the proxy question. There are three options for addressing the proxy issue when developing a measure of pediatric HRQL, and each has advantages and disadvantages that must be weighed when designing a study. Whenever a child is able to provide reliable and valid data, the child's self-report is the ideal strategy because it is consistent with the definition of HRQL, which emphasizes the patient's subjective perspective. Furthermore, it is important to consider the child's perceptions to provide treatments that will have the most positive impact in multiple domains, including contexts that may be unknown to parents such as school or daycare [10].

The disadvantage of child-report instruments is that children, particularly at younger ages, may not be able to provide reliable information on complex or abstract health-related constructs. Thus, before implementing a child-report HRQL measure, researchers will need to evaluate the age appropriateness of the instrument, including the vocabulary, instructions, sentence structure, content, and response options. If the researchers believe that it is essential to assess the subjective views of younger children, but they are concerned about developmental limitations, one option is to develop an interviewer-administered instrument. A structured interview can include standardized procedures for teaching children how to respond to the measure, instructing children not to answer questions they do not understand, and checking children's comprehension of items. Although an interviewer-administered instrument will be more costly to use than a self-report questionnaire, structured interview methodology may help younger children provide more reliable and valid data.

For assessment of more complex constructs, it may be necessary to use an adult as a proxy respondent. In comparison to children, adults can generally be expected to provide more reliable information on more complex, abstract, psychologically oriented concepts. Parents are the most common proxy respondents, and there is evidence suggesting that parent reports are more accurate than those given by physicians or nurses [40]. For very young or severely disabled children, parents may provide valuable information that would otherwise be unobtainable. In addition, the parent's perspective is important in itself because of the dependent nature of the parent–child relationship. It is the parent who typically assesses the impact of the child's health and decides whether the child will receive treatment. The parent can also provide valuable information on the impact of the child's illness and treatment on family functioning, which is an integral part of children's HRQL.

There are several disadvantages of using parents as proxy respondents. First, a proxy report is somewhat inconsistent with the concept of HRQL, which is defined according to the patient's subjective view. Thus, it may be theoretically sound to have parents report on a child's "health status," but not specifically on a child's HRQL. Second, the proxy method raises questions concerning which parent to use and whether mother and father reports can be considered equivalent [9,32]. In longitudinal trials with parent proxies, it is recommended that the same parent provide the reports across the study to avoid systematic error resulting from differences between the two parents. Third, it is likely that parents' reports of a disease's impact on their children will be biased by how the parents themselves are affected. Finally, it is not always clear whether parents are the most appropriate adult proxy respondent [32]. Some children may spend more time with a teacher, daycare provider, or other family member than with a parent, and this other adult may have more accurate insight into the child's social and psychological functioning.

Because neither the child's self-report nor the parent's proxy report is without risk, some researchers have suggested obtaining information from both the child and a parent [27,29]. This approach may provide the most complete picture of how a disease or treatment impacts the lives of children and their families. Nevertheless, it will be more costly to collect data from both sets of respondents rather than choosing one, and this strategy raises several methodological questions. For example, researchers will have to decide whether to pool data

from the two respondents or interpret their data separately. Another potential problem is the question of how to interpret findings when parents and children's reports diverge. It is difficult to determine whose reports are more accurate because parent report may be expected to have greater reliability, but child report may have more validity given the subjective nature of HRQL. One possible approach in a clinical trial is to assess both child and parent reports, but to determine a priori that one will be the primary HRQL endpoint of a clinical trial. For younger children, it may be best to choose parent report as the primary endpoint, but also assess the child's self-report which can provide additional information on HRQL.

In conclusion, there is not a solution to the proxy question that will be correct for every clinical trial. Consequently, it is recommended that researchers carefully examine the costs and benefits of each possible approach during instrument development, before pivotal studies. The decision of whether to use child-report, parent-report, or both requires consideration of numerous factors including the child's age, the domains of HRQL that may be addressed, the disease area, the study design, and the intended use of the data.

Age-Appropriate Instrument Formatting and Design

Several previous reviews of pediatric health outcomes assessment have discussed aspects of instrument formatting and design that can be adjusted depending on the age of the respondents [10,11,28,29,32,41,42]. The specific design and format of each pediatric HRQL instrument will depend on numerous factors including the content of the items and the ages of the intended respondents. Thus, it is recommended that instruments be pilot tested so that formatting and administration procedures can be evaluated before using the measure with a large sample. Cognitive debriefings, in which children are asked to comment on instruments, can also provide important information regarding the age appropriateness of items before using an instrument in pivotal studies [43,44]. The following are five issues to consider when developing a measure of pediatric HRQL.

Likert scales. There are developmental differences in children's ability to understand and respond to items rated on Likert scales. Eight-year-old children have been shown to accurately use the full range of 5- and 7-point Likert scales to rate their health status, whereas younger children tend to use more extreme responses [33,45]. When using Likert scales with younger children, the response options can be creatively designed to help them understand the task. For example, circles of graduated sizes and illustrations to anchor the extreme responses can be used as visual aids, as demonstrated in Figure 2 [33].

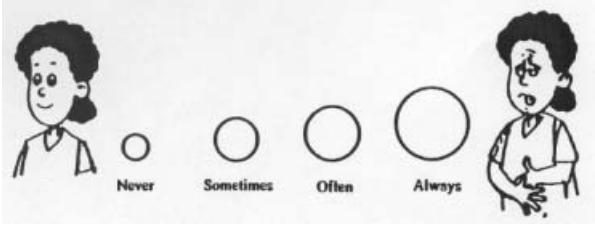


Figure 2 Response options with anchoring illustrations from the Child Health and Illness Profile (CHIP) [33].

Recall periods. Age-related differences have also been demonstrated in children's ability to accurately report on their health status within a specific recall period. Eight-year-old children have been shown to use a 4-week recall period with reasonable accuracy, but younger children may have difficulty with the concept of 1 week or 1 month [33,45]. One strategy for helping younger children understand this task is to tie the recall period to a concrete event that they would remember [45]. For example, children can be asked to rate their health status since their last doctor's appointment 1 week ago.

Length of the instrument. The length of a questionnaire or interview for children requires careful consideration and pilot testing because of the wide variation in children's ability to maintain attention to tasks. Generally, older children can be expected to complete longer measures than younger children.

Children's degree of independence during administration. It may be necessary to adjust administration procedures for different ages. Younger children may require interviewers to assist them with reading questionnaires, understanding administration procedures, and staying focused on the task. Older children can be expected to complete written questionnaires with greater independence.

Formatting details. When designing child-report measures, it is particularly important to attend to details of formatting, such as maintaining a clear layout of items and using larger print for younger children.

Creating Multiple Forms of a Measure Corresponding to Different Age Groups

Bibace and Walsh [46] demonstrated that children's understanding of illness develops in stages consistent with Piaget's theory of cognitive development. Piaget proposed that children's causal reasoning is guided by logic different from that of adults, and this logic develops in a series of sequentially ordered stages [47]. By applying this theory, Bibace and Walsh derived and tested stages for children's conceptions of illness, beginning with early prelogical stages typical of children between 2 and 6 years old who are unable to explain the causes of illness. By approximately 11 years of age, many children have progressed to formal-logical thinking, which is characterized by a conception of the causal sequence of physiological mechanisms. In the final stage, children demonstrate an understanding that a person's thoughts and feelings can affect physical functioning. This research was intended to help physicians and health educators communicate more effectively with children, and the findings have provided a theoretical and empirical foundation for health education curricula on AIDS/HIV and smoking [48–50]. This work on children's conceptions of illness can also be applied to measure development for clinical trials in which children are asked to report their health and HRQL.

One strategy for addressing these developmental differences is to create multiple forms of a child-report instrument, each designed for a different age group. When designing multiple forms, a researcher will need to determine appropriate age groupings and ways that the forms will differ from each other. An example of an instrument that uses this multiple form approach is the Childhood Asthma Questionnaire (CAQ) [31,51]. This measure was designed to evaluate treatments by assessing children's feelings about their everyday lives and their asthma. Three child-report forms were developed, intended for children ages 4 to 7, 8 to 11, and 12 to 16 (see Table 1). Forms for older age ranges are longer with more response options and more complex HRQL domains. For example, Form C (ages 12 to 16) is specifically designed to correspond to the abilities, interests, and social relationships of adolescents.

The advantage of this multiple form approach is that it takes into account children's developmental differences, including their conception of illness as well as its cause and impact. With this strategy, it is possible to design a series of questionnaires that assess the same general constructs, while ensuring that formatting and content are age appropriate for all children. Nevertheless, this approach also raises some methodological and practical challenges. For example, because the forms contain different items and domains, data cannot be pooled across age groups. If analyses are conducted separately for the different age groups, it will be necessary to collect a sample that is large enough to ensure sufficient statistical power for each age group. Before developing or using multiple forms of an instrument, researchers will need to evaluate whether they have sufficient time and financial resources for the additional data collection and analyses that will be required.

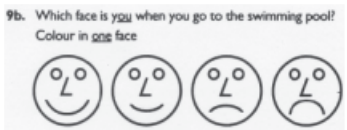
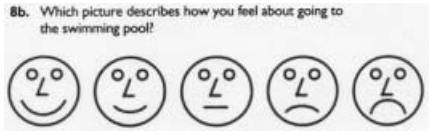
Avoiding Child Response Sets

When responding to questionnaires or interviews, children may have a proclivity for a response set, which is a tendency to provide a certain type of response regardless of the question. Response sets are problematic because they can cause data to be biased, skewed, or simply inaccurate. Consequently, response sets can introduce systematic error into the data that may mask meaningful or statistically significant findings.

Examples of response sets that are believed to be more common among children than adults include responding with the intent to please the interviewer or answering questions they do not understand in an attempt to appear competent [10,29]. In addition, some children may have a tendency to provide repetitive responses (e.g., consistently choosing the same number on a scale), particularly when a measure repeatedly uses the same scaling system [29]. A common child response set with demonstrated developmental differences is the tendency to provide extreme answers (e.g., responding only with 1 or 5 on a series of 5-point Likert scales), which is primarily a risk with younger children. Children ages 5 to 6 have been shown to provide significantly more extreme responses than children ages 7 to 8 when using a Likert scale [33].

Response sets can be minimized through careful instrument development and study design. One strategy is to assess some constructs twice within a single measure, once with a positively voiced item and once with a negatively voiced item (e.g., "I have been sick during the past 2 weeks" and "I have been healthy during the past 2 weeks"). Children who answer with repetitive response sets may be identified if they provide contradictory answers to the two items. Similarly, HRQL can be assessed with more than one instrument in a given study, possibly using both a generic and a disease-specific measure.

Table I A condition-specific measure of HRQL with multiple forms corresponding to different age groups: The Childhood Asthma Questionnaire [31,51]

	Form		
	A	B	C
Ages (years)	4–7	8–11	12–16
Number of Items	14	22	31
Administration	Requires parent assistance	Independent self-report	Independent self-report
Domains	1. Quality of living 2. Distress	1. Active quality of living 2. Passive quality of living 3. Distress 4. Severity	1. Active quality of living 2. Teenage quality of living 3. Distress 4. Severity 5. Reactivity
Sample Items and response options			How do you feel about telling other people you have asthma? 

Correlations between similar scales on the two measures can then be used to detect inconsistent reporting. When designing a pediatric study, it is also important to consider the length and number of measures. Younger children, in particular, may begin to rely on response sets and provide inaccurate responses if the length of an assessment exceeds their attention span or patience.

During data collection, project staff can be trained to recognize common child response sets. These staff members should review children's responses following independent questionnaire completion and carefully consider children's responses during interviews. Then, instances in which the child appears unwilling or unable to respond correctly should be documented. This documentation can provide justification for excluding the participant's data in the analyses.

During data analysis, it is important to remain aware that some children's data may reflect response sets. Examination of scatter plots and frequency tables is often helpful in detecting children who have provided invalid data. If there is sufficient evidence that a child did not respond accurately, this child can be considered an "outlier," and it will be preferable to exclude these data from the analyses (for outlier criteria, see Bollen and Jackman [52] and Neter et al. [53]).

For phase III and IV clinical trials, criteria for identifying these outliers should be specified a priori based on experience with the instrument during instrument development and earlier phase trials. During these earlier studies, it may be possible to identify the common response sets for a given measure, the ages at which children are most likely to respond inaccurately, and an expected percentage of children that may have these difficulties. If a substantial number of children are expected to demonstrate response sets, researchers can oversample to ensure sufficient sample size and statistical power after outliers are dropped from the analysis data set.

Selected Generic and Condition-Specific HRQL Measures for Use in Pediatric Populations

Both generic and condition-specific measures have been developed to assess HRQL in children (for thorough reviews of existing measures, see Eiser and Morse [9,54]). As is true for adults, generic measures are useful to compare HRQL across various populations, which may include patients who vary in terms of their medical conditions. Consequently, generic measures can be used to compare the HRQL impact of various diseases. In addition, data from patients with a specific disease can be compared to general pediatric population norms to determine the impact of the disease on HRQL. For example, normative data for the Child Health Questionnaire are available, including norms for groups divided by age, sex, and medical conditions. Generic measures have been developed for children from 0 to 18 years old, using both parent and child report (see Table 2 for a selection of Generic HRQL measures) [35,39,55–62].

Condition-specific measures take into account aspects of disease and treatment that are relevant to specific medical conditions. Compared to generic measures, these measures tend to be more sensitive to changes, and they may be more effective at detecting treatment effects. Therefore, they are often used in clinical trials. Condition-specific pediatric measures are available for a number of medical conditions, such as asthma, allergic rhinitis, cancer, diabetes, epilepsy, juvenile arthritis, Crohn's disease, and spina bifida (see Table 3 for a selection of disease-specific HRQL measures) [15,31,51,63–71]. Only one condition-specific HRQL measure was located that was developed for a psychiatric disorder in children (the ADHD Impact Module) [72].

Recommendation for Future Research: The Impact of Psychiatric Disorders on Pediatric HRQL

To date, research on pediatric HRQL has focused almost exclusively on medical diseases, with little attention given to psychiatric disorders. Studies conducted with adults suggest that a range of psychiatric disorders including schizophrenia, depression, bipolar mood disorder, and anxiety disorders significantly impair HRQL [73–76]. Furthermore, clinical trials have found that treatment of these psychiatric disorders can improve HRQL [77,78]. Despite the fact that mental health problems are also common in children [79], little research has examined the HRQL impact of psychiatric disorders in pediatric populations.

The limited available data in this area suggest that a range of psychiatric disorders have a significant negative impact on children's HRQL [80]. Furthermore, results of one clinical trial indicate that treatment of attention-deficit/hyperactivity disorder, one example of a psychiatric disorder, can significantly improve psychosocial aspects of HRQL [81]. Given these initial findings, it is recommended that

Table 2 Selected generic HRQL measures

Measure	Reference	Reporter (age group)	Number of items	Subscales
Child Health and Illness Profile–Adolescent (CHIP–AE)	Starfield et al. [55]	Self (11–17)	153	Satisfaction, Achievement, Disorders, Risks, Discomfort, Resilience
Child Health Questionnaire (CHQ)	Landgraf et al. [56]	Self (10–19) Parent (4–19)	87 Multiple versions including: 28, 50, 98	Physical Functioning, Role/Social Emotional,* Role/Social Behavioral,* Role/Social Physical, Bodily Pain, General Behavior, Mental Health, Self-Esteem, General Health Perceptions, Change in Health, Parental Impact-Emotional, Parental Impact-Time, Family Activities, Family Cohesion
Child Quality of Life Questionnaire (CQOL)	Graham et al. [57]	Self and Parent (9–15)	15	Getting About and Using Hands, Out of School Activities, Friends, Family Relationships, Discomfort Due to Bodily Symptoms, Worries, Depression, Seeing, Communication, Eating, Sleep, Appearance
Functional Status II-R (FSIIR)	Stein and Jessop [58]	Parent (0–16)	Multiple versions including: 14 and 43	Communication, Mobility, Mood, Energy, Sleeping, Eating, Toileting, Play
KINDL (German generic quality of life instrument for children)	Ravens-Sieberer and Bullinger [59]	Self (8–16)	40	Mental, Physical, Social Life, Psychologic Well Being, Social Relationships, Physical Functioning, Everyday Life Activities
Pediatric Quality of Life Questionnaire (PedsQL)	Varni et al. [60]	Child (8–12) Adolescent (13–18) Parent (8–18)	15 items comprising 3 core scales 30 additional items comprising 8 modules	Physical Functioning, Psychologic Functioning Scale, Social Functioning Scale, Pain, Nausea, Procedural Anxiety, Treatment Anxiety, Worry, Cognitive Problems, Perceived Physical Appearance, Physician/Nurse Communication
TNO-AZL Child Quality of Life Questionnaire (TACQOL)	Verrips et al. [61] Vogels et al. [35] Theunissen et al. [39]	Self (8–15) Parent (5–15)† Parent (6–15)‡	56	Physical Complaints, Motor Functioning, Autonomous Functioning, Social Functioning, Cognitive Functioning, Positive Moods, Negative Moods
TNO-AZL Preschool Children Quality of Life Questionnaire (TAPQOL)	Fekkes et al. [62]	Parent (1–5)	43	Physical Functioning (sleep, appetite, lung problems, stomach problems, skin problems, motor functioning), Social Functioning (problem behavior, social functioning), Cognitive Functioning (communication), Emotional Functioning (positive mood, anxiety, liveliness)

*These two scales are combined in the 28- and 50-item versions.
†Verrips et al. [61].
‡Vogels et al. [35].

further research be conducted to examine the impact of psychiatric disorders and treatment on children's HRQL.

Conclusions

The FDA and pharmaceutical companies have recently demonstrated increasing awareness of the need for additional understanding of drug treatment effects among children. In the pediatric health outcomes literature, there is growing consensus that HRQL instruments are an essential complement to clinical symptom measures in providing a comprehensive picture of children's health status. As more pediatric clinical trials have been initiated, however, researchers have encountered a unique set of challenges involved in assessing HRQL among children, such as identifying the age at which children can reliably report various domains of HRQL and determining whether children or their parents are the best respondents. Reliable and valid assessment of HRQL will require thorough planning and instrument development, including pilot testing and cognitive debriefing. Careful attention to the details of instrument development and study design will lead to a greater understanding of the broad impact of disease and treatment among pediatric populations. The results

Table 3 Selected condition-specific HRQL measures

Measure	Reference	Reporter (age group)	Number of Items	Subscales
Asthma				
Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	Juniper et al. [15]	Self (7–17)	23	Activity Limitations, Symptoms, Function
Childhood Asthma Questionnaire (CAQ)	Christie et al. [51] French et al. [31]	Self: CAQ-A (4–7 years) CAQ-B (8–11 years) CAQ-C (12–16 years)	 14 22 31	 CAQ-A: Distress CAQ-B: Active QoL, Passive QoL CAQ-C: Active QoL, Teenage QoL, Distress, Severity, Reactivity
Allergic rhinitis				
Pediatric Rhino-conjunctivitis Quality of Life Questionnaire (PRQLQ)	Juniper et al. [63]	Self (6–12)	23	Nose Symptoms, Eye Symptoms, Practical Problems, Other Symptoms, Activity Limitations
Adolescent Rhino-conjunctivitis Quality of Life Questionnaire (AdolRQLQ)	Juniper et al. [64]	Self (12–17)	25	Practical Problems, Non–Hay Fever Symptoms, Nose Symptoms, Eye Symptoms, Patient-Specific Activities, Emotions
Cancer				
Pediatric Oncology Quality of Life Scale (POQOLS)	Goodwin et al. [65]	Parent (0–18)	21	Physical Functioning, Emotional Distress, Externalizing Behavior
Pediatric Cancer Quality of Life Inventory (PCQL)	Varni et al. [66]	Self and Parent (8–18)	32	Disease- and Treatment-Related Symptoms, Physical Functioning, Psychological Functioning, Social Functioning, Cognitive Functioning
Epilepsy				
Quality of Life in Epilepsy (adapted from QOLIE-89)	Wildrick et al. [67]	Self (8–18)	25	Self-Concept, Home Life, School Life, Social Activities, Medicines
Diabetes				
Diabetes Quality of Life Instrument (DQOL) adapted for older children and adolescents	Ingersoll and Marrero [68]	Self (11–18)	53	Disease Impact, Disease-Related Worries, Satisfaction with Life
Arthritis				
Juvenile Arthritis Quality of Life Questionnaire	Duffy et al. [69]	Self (9–18) Parent (2–18)	74 74	Gross Motor Function, Fine Motor Function, Psychosocial Function, General Symptoms
Crohn's disease				
Quality of Life in Children with Crohn's Disease	Rabbett et al. [70]	Self (8–17)	88	Disease and Its Treatment, Social, Emotional, Family, Education, Future Aspects
Spina bifida				
Quality of Life in Spina Bifida Questionnaire	Parkin et al. [71]	Self (13–20) Parent (5–12)	47 44	Social, Emotional, Intellectual, Financial, Medical, Independence, Environmental, Physical, Recreational, Vocational

of this research can guide development of treatments that will improve children's HRQL.

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