

# Literature Review: Health-related Quality of Life Measurement in Pediatric Oncology: Hearing the Voices of the Children

James W. Varni,<sup>1</sup> PhD, Christine Limbers,<sup>2</sup> MS, and Tasha M. Burwinkle,<sup>3</sup> PhD

<sup>1</sup>Department of Pediatrics, College of Medicine, Department of Landscape Architecture and Urban Planning, College of Architecture and <sup>2</sup>Department of Psychology, Texas A&M University, College Station and <sup>3</sup>The Children's Hospital at Scott and White, Department of Pediatrics, College of Medicine, Texas A&M University Health Sciences Center

**Objectives** The objective of this literature review is to provide an overview of the evidence for pediatric patient self-report in pediatric oncology. **Methods** A review of the general literature on pediatric health-related quality of life (HRQOL) measurement as background, with pediatric patient self-report data from the *Journal of Pediatric Psychology* during the past 5 years in pediatric oncology summarized. Utilizing the PedsQL™ (available at <http://www.pedsq.org>), data are presented to illustrate child and parent reports in pediatric oncology. **Results** Data demonstrate that children as young as 5 years of age can reliably and validly self-report their HRQOL when an age-appropriate instrument is utilized. **Conclusions** The evidence supports including pediatric patients' perspectives in clinical trials. Parent proxy-report is recommended when pediatric patients are too young, too cognitively impaired, too ill or fatigued to complete a HRQOL instrument, but not as a substitute for child self-report when the child is willing and able to provide their perspective.

**Key words** children; health-related quality of life; patient-reported outcomes; pediatric oncology; PedsQL.

The last decade has evidenced a dramatic increase in the development and utilization of pediatric health-related quality of life (HRQOL) measures in an effort to improve pediatric patient health and determine the value of health care services (Matza, Swensen, Flood, Secnik, & Leidy, 2004; Varni, Burwinkle, & Lane, 2005). An HRQOL instrument must be multidimensional, consisting at the minimum of the physical, mental, and social health dimensions delineated by the World Health Organization (World Health Organization, 1948). Although the term "quality of life" (QOL) is sometimes used interchangeably with HRQOL, QOL is actually a broader construct that encompasses aspects of life which are not amenable to health care services. Thus, HRQOL has emerged as the most appropriate term for QOL health dimensions which are within the scope of health care services [Food and Drug Administration (FDA), 2006].

Although the measurement of HRQOL in pediatric oncology has been advocated for a number of years

(Mulhern et al., 1989), the emerging paradigm shift toward patient-reported outcomes (PROs) in clinical trials (FDA, 2006) has provided the opportunity to further emphasize the value and essential need for pediatric patient self-reported PRO measurement as health outcomes in pediatric oncology clinical trials (Razzouk et al., 2006).

## Patient-Reported Outcomes in Pediatric Clinical Trials

During the past several years, legislative changes have created both voluntary and mandatory guidelines for drug studies in children, resulting in a substantial increase in pediatric clinical trials. Under the Pediatric Exclusivity Provision of the Best Pharmaceuticals for Children Act (BPCA), reauthorized in 2002, companies that conduct drug studies with children, as requested by the FDA, are eligible for an additional 6 months of marketing exclusivity

All correspondence concerning this article should be addressed to James W. Varni, PhD, Professor of Architecture and Medicine, College of Architecture, Texas A&M University, 3137 TAMU, College Station, Texas, 77843-3137 USA.  
E-mail: [jvarni@archmail.tamu.edu](mailto:jvarni@archmail.tamu.edu).

*Journal of Pediatric Psychology* 32(9) pp. 1151–1163, 2007

doi:10.1093/jpepsy/jsm008

Advance Access publication March 8, 2007

*Journal of Pediatric Psychology* vol. 32 no. 9 © The Author 2007. Published by Oxford University Press on behalf of the Society of Pediatric Psychology. All rights reserved. For permissions, please e-mail: [journals.permissions@oxfordjournals.org](mailto:journals.permissions@oxfordjournals.org)

for the studied drug. The Pediatric Research Equity Act (PREA), signed in 2003, allows the FDA to require pediatric studies if it is determined that the product is likely to be used by a considerable number of pediatric patients, or the product would offer an important advantage to pediatric patients over existing treatments. Nevertheless, while the above pediatric initiatives have opened the opportunity for children to be included in clinical trials, pediatric patients have not been afforded the right to self-report on matters pertaining to their health and well-being when evaluating the health outcomes of treatments in the majority of pediatric clinical trials to date (Clarke & Eiser, 2004). This fact stands in sharp contrast to the recent FDA Draft Guidance for Industry in which the FDA describes how it evaluates PRO instruments as health outcomes in clinical trials (FDA, 2006). In the Draft Guidance for Industry, the FDA is quite definitive in stating that “some treatment effects are known only to the patient.” Thus, what has been an obvious recognition in clinical trials for adult patients (i.e., that PROs are *patient self-reported* outcomes), has not received the same level of recognition in clinical trials for pediatric patients (Clarke & Eiser, 2004).

### Patient Reported-Outcomes (PROs)

By definition, PROs are self-report instruments that directly measure the patient’s perceptions of the impact of disease and treatment as clinical trial endpoints (FDA, 2006). PROs include multi-item HRQOL instruments, as well as single-item symptom measures [e.g., pain visual analog scale (VAS)] (Acquadro et al., 2003; Sherman, Eisen, Burwinkle, & Varni, 2006; Willke, Burke, & Erickson, 2004). Research conducted in the 1980s and early 1990s clearly demonstrated that children as young as 5 years of age can self-report their pain intensity using standardized VAS instruments (McGrath, 1990; Varni, & Bernstein, 1991; Varni, Thompson, & Hanson, 1987), establishing pediatric patient self-report of pain intensity as the standard for clinical research and practice.

### The Proxy Problem

It is well documented in both the adult and pediatric literature that information provided by proxy-respondents is not equivalent to that reported by the patient (Achenbach, McConaughy, & Howell, 1987; Sprangers & Aaronson, 1992). Imperfect agreement between self-report and proxy-report, termed cross-informant variance (Varni, Katz, Colegrove, & Dolgin, 1995), has been consistently documented in the PRO measurement of children with

chronic health conditions, including pediatric cancer, and healthy children (Chang & Yeh, 2005; Clancy, McGrath, & Oddson, 2005; Felder-Puig et al., 2006; Levi & Drotar, 1999; Vance, Morse, Jenney, & Eiser, 2001; Varni et al., 1998; Varni, Seid, & Rode, 1999).

In a meta-analysis of studies evaluating the agreement between child self-report and parent proxy-report on different measures of HRQOL, Eiser & Morse (2001) found generally good agreement ( $r > .50$ ) between child and parent reports for domains reflecting physical activity, functioning and some symptoms, but generally poor agreement ( $r < .30$ ) between child self-report and parent proxy-report for emotional and social HRQOL domains (Eiser & Morse, 2001). Given these correlations, and others like them in the literature cited above, it can be concluded that parent proxy-reports typically explain only 10–25% of the variance in child self-report HRQOL outcomes. Thus, the findings on the *proxy problem* “indicate that parent reports cannot be substituted for child reports” (Theunissen et al., 1998). To further complicate the use of proxy reporters, which typically are the child’s parents, most often mothers, are the unresolved concerns regarding the influence of parental distress and related factors on parents’ perceptions of child health and well-being (Berg-Nielsen, Vika, & Dahl, 2003; De Los Reyes & Kazdin, 2004; Richters, 1992). Taken together, the evidence is quite compelling that evaluations of pediatric patients’ perspectives regarding treatment outcomes should be included in pediatric clinical trials given the documented differences between child and parent reports.

### The Role for Parent Proxy-Report

While pediatric patient self-report should be considered the standard for measuring perceived HRQOL, there may be circumstances when the child is too young, too cognitively impaired, too ill or fatigued to complete a HRQOL instrument, and parent proxy-report may be needed in such cases (Hays et al., 2006). Further, it is typically parents’ perceptions of their children’s HRQOL that influence health care utilization (Campo, Comer, Jansen-McWilliams, Gardner, & Kelleher, 2002; Janicke, Finney, & Riley, 2001; Varni & Setoguchi, 1992). Thus, HRQOL instruments should be selected that measure the perspectives of both the child and the parent, since these perspectives may be independently related to health care utilization, risk factors, and quality of care (Varni et al., 2005). However, parent proxy-report should be included

to complement pediatric patient self-report, not to serve as a convenient substitute for pediatric patient self-report.

In cases in which pediatric patients are not able to provide self-report, reliable and valid parent proxy-report instruments are needed (Varni, Limbers, & Burwinkle, 2007b). For example, in a recent HRQOL study with pediatric patients with brain tumors, of those children aged 5–18 years who were age eligible to self-report, 62% of the children were able to self-report (Palmer, Meeske, Katz, Burwinkle, & Varni, 2007). Of the 99 families of children aged 2–18 years who participated in this study of pediatric brain tumor patients, parent proxy-report was obtained from 99 parents, while pediatric patients who did not provide self-report included 17 patients who were toddlers (ages 2–4 years), 7 patients who reported they felt too ill to participate when approached, 11 who were determined to be cognitively delayed and unable to provide self-report, 5 who refused, and 4 who attempted to fill out the forms and became fatigued or became ill during the interview and were unable to finish during their clinic visit. As is clear from this study and others, parent proxy-report instruments are required in situations such as this, and reliable and valid parent proxy-report instruments are consequently vital when children are unable to provide self-report.

Research on the factors which may influence the level of agreement between pediatric patients and their parents is also emerging, with age and health status as potential factors among others (Cremeens, Eiser, & Blades, 2006b). For example, some findings in pediatric oncology suggest that parent proxy-report demonstrates higher agreement with child self-report when pediatric patients with cancer are off-treatment rather than on-treatment, with parent proxy-report underestimating the negative impact of cancer treatment on HRQOL relative to pediatric patient self-report (Yeh, Chang, & Chang, 2005). Ideally, parent and child HRQOL instruments should measure the same constructs with parallel items in order to make comparisons between self- and proxy-report more meaningful (Cremeens, Eiser, & Blades, 2006a; Russell, Hudson, Long, & Phipps, 2006).

### Generic and Disease-Specific HRQOL Instruments

While there are a number of pediatric oncology disease-specific instruments available (Eiser, 2004; Nathan, Furlong, & Barr, 2004), there are potential benefits of integrating generic and disease-specific approaches (Patrick & Deyo, 1989; Sprangers, Cull, Bjordal,

Groenvold, & Aaronson, 1993; Varni et al., 1999). Disease-specific measures may enhance measurement sensitivity for health domains germane to a particular chronic health condition, while a generic HRQOL measurement instrument enables comparisons across pediatric populations and facilitates benchmarking with healthy population norms. Thus, there is an emerging perspective that for pediatric chronic health conditions, both generic and disease-specific HRQOL measures should be administered so as to gain a more comprehensive evaluation of the patient's HRQOL.

### Literature Review of Pediatric Oncology Studies in the *Journal of Pediatric Psychology*

A literature review was conducted in the *Journal of Pediatric Psychology* from January 2002 to January 2007 for studies that assessed the HRQOL or QOL of pediatric cancer patients or survivors during that 5-year period. A measure was designated as a HRQOL or QOL instrument if the author(s) defined it as such and it was multi-dimensional, consistent with guidelines set forth by the World Health Organization (World Health Organization, 1948). Studies were excluded from this review that measured the HRQOL or QOL of parents or siblings of pediatric cancer patients or survivors. The primary purpose of this review was to examine the ages at which HRQOL or QOL were measured for pediatric cancer patients and survivors by child self-report and parent proxy-report in the *Journal of Pediatric Psychology* for the most recent 5-year period.

Table I presents the findings of this literature review. A total of five studies published in the *Journal of Pediatric Psychology* between January 2002 and January 2007 were identified by this search process. While three of the five studies assessed the HRQOL or QOL of pediatric cancer patients and survivors from both the perspective of the child and parent, these studies did not include child self-report for children under the age of 8 years (Barakat et al., 2003; De Clercq, De Fruyt, Koot, & Benoit, 2004; Schwartz & Drotar, 2006). In the two studies in which HRQOL or QOL were measured for pediatric cancer patients and survivors under the age of 8 years, only parent proxy-report was obtained, with the lower age limit of 5 years (Drotar, Schwartz, Palermo, & Burant, 2006; Parsons et al., 2006).

Table II presents characteristics of individual studies published in the *Journal of Pediatric Psychology* from January 2002 to January 2007 measuring outcomes not labeled by the author(s) as HRQOL or QOL in pediatric

**Table 1.** Characteristics of Individual Studies Published in the *Journal of Pediatric Psychology* from January 2002 to January 2007 Measuring the HRQOL or QOL of Pediatric Cancer Patients and Survivors

Study	<i>n</i>	Cancer diagnosis	Child self-report/age	Parent proxy-report/age	Measures
Barakat et al. (2003)	13	Brain tumors	Child self-report for ages 8–14 years	Parent proxy-report for ages 8–14 years	Miami Pediatric Quality of Life Questionnaire (MPQLQ)
De Clercq et al. (2004)	67	Survivors of lymphoblastic and acute nonlymphoblastic leukemia ( <i>n</i> = 30), Hodgkin's disease and non-Hodgkin's lymphoma ( <i>n</i> = 8), and solid tumors including brain tumors ( <i>n</i> = 29)	Child self-report for ages 8–13 years	Parent proxy-report for ages 8–13 years	Pediatric Quality of Life Inventory™ (PedsQL™) 4.0 Generic Core Scales
Drotar et al. (2006)	33	Cancer diagnoses not specified	None	Parent proxy-report for ages 5–18 years	Child Health Questionnaire (CHQ-PF-50)
Schwartz & Drotar (2006)	57	Acute lymphoblastic leukemia ( <i>n</i> = 15), acute myelogenous leukemia ( <i>n</i> = 4), Hodgkin's lymphoma ( <i>n</i> = 12), non-Hodgkin's lymphoma ( <i>n</i> = 8), and other cancers ( <i>n</i> = 18)	Self-report for young adults ages 18–28 years	None	SF-36
Parsons et al. (2006)	160	Hematopoietic stem cell transplant	None	Parent proxy-report for ages 5–20 years	Child Health Ratings Inventories (CHRIs) and the Disease Impairment Inventory (DSII)-HSCT module

**Table II.** Characteristics of Individual Studies Published in the *Journal of Pediatric Psychology* from January 2002 to January 2007 Measuring Outcomes Not Labeled as HRQOL or QOL of Pediatric Cancer Patients and Survivors

Study	<i>n</i>	Cancer diagnosis	Child self-report/age	Parent proxy-report/age	Measures
Johnston et al. (2003)	116	Pediatric cancer patients on active treatment for cancer; cancer diagnoses not specified	Child self-report for ages 7–18 years	Parent proxy-report for ages 7–18 years	A modified version of the Coddington Life Events Questionnaire (CLEQ)
Steele et al. (2004)	68	Leukemia (53.8%), lymphomas/Hodgkin's disease (9.2%), solid tumors (16.9%), central nervous system malignancies (16.9%), other malignancies (3.1%)	None	Parent proxy-report for ages 4–13 years	Mood/Behavior and Somatic Distress subscales of the Behavioral, Affective, and Somatic Experiences Scale (BASES)
Klosky et al. (2004)	79	Pediatric cancer patients receiving radiation therapy (RT); cancer diagnoses not specified	None	Trained clinical observers for ages 2–7 years	Observed Behavioral Distress (OBD)
Dahlquist & Pendley (2005)	29	Pediatric cancer patients undergoing chemotherapy; cancer diagnoses not specified	None	Parent proxy-report and nurse-report for ages 29–62 months	The Observation Scale of Behavior Distress (OSBD)
Tyc et al. (2005)	90	Leukemias/lymphomas ( <i>n</i> = 44), solid tumors ( <i>n</i> = 27), and brain tumors ( <i>n</i> = 19)	Self-report for ages 12–18 years	None	Smoking Status, and Smoking Survey which included measures of intentions to smoke, and tobacco-related psychosocial risk factors
Helton et al. (2006)	150	Long-term survivors of acute lymphocytic leukemia ( <i>n</i> = 76) and brain tumors ( <i>n</i> = 74)	None	Parent proxy-report and teacher-report for ages 6–18 years	Conners' Rating Scales-Revised: Short Forms (CRS-R:S); Achenbach Child Behavior Checklist (CBCL)
Reeves et al. (2006)	38	Survivors of childhood medulloblastoma (MB)	Tests administered to children and adolescents ages 6 years and older	None	California Verbal Learning Test, Child Version (CVLT-C); Conners' Continuous Performance Test (CPT); Wechsler Individual Achievement Test (WIAT)

(continued)

Table II. Continued

Study	<i>n</i>	Cancer diagnosis	Child self-report/age	Parent proxy-report/age	Measures
Stoppelbein et al. (2006)	39	Survivors of acute lymphoblastic leukemia (50%) and other cancers (50%)	Child self-report for mean age of 12.79 years (SD = 2.81); age ranges not given	Parent proxy-report for mean child age of 12.79 years (SD = 2.81); age ranges not given	Child Posttraumatic Stress Disorder Reaction Index (CPTSD-RI); Revised Children's Manifest Anxiety Scale (RCMAS); Children's Depression Inventory (CDI); Perceived Future Threat
Phipps et al. (2006)	162	Pediatric cancer patients and young adult survivors diagnosed with or once diagnosed with acute lymphocytic leukemia ( <i>n</i> = 48), other leukemia ( <i>n</i> = 20), Hodgkin's disease/non-Hodgkin's lymphoma ( <i>n</i> = 28), and solid tumors/brain tumors ( <i>n</i> = 66)	Self-report for ages 7–17 years for groups 1, 2, and 3; ages 18 years and older for group 4	Parent proxy-report for ages 7–17 years for groups 1, 2, and 3	UCLA PTSD Index (PTSDI); Impact of Events Scale-Revised (IES-R); Children's Social Desirability Scale (CSD); The State-Trait Anxiety Inventory for Children (STAIC)
Barakat et al. (2006)	150	Survivors of leukemias (30.5%), solid tumors (35.1%), lymphomas (21.2%), and other cancers (13.2%)	Child self-report for ages 11–19 years	Parent proxy-report for ages 11–19 years	Perceptions of Changes in Self (PCS) scale from the Impact of Traumatic Stressors Interview Schedule (ITSIS); Assessment of Life Threat and Treatment Intensity Questionnaire (ALTTIQ); Impact of Events Scale-Revised (IES-R)

cancer patients and survivors. Consistent with the findings above, the majority of studies assessed a limited age range for child self-report, especially for the youngest children (Barakat, Alderfer, & Kazak, 2006; Dahlquist & Pendley, 2005; Helton, Corwyn, Bonner, Brown, & Mulhern, 2006; Johnston, Steele, Herrera, & Phipps, 2003; Klosky et al., 2004; Phipps, Larson, Long, & Rai, 2006; Reeves et al., 2006; Steele, Dreyer, & Phipps, 2004; Stoppelbein, Greening, & Elkin, 2006; Tyc, Lensing, Klosky, Rai, & Robinson, 2005).

To summarize, no HRQOL or QOL pediatric oncology studies published in the *Journal of Pediatric Psychology* for the most recent 5-year period included child self-report for children younger than 8 years of age or parent proxy-report for children younger than 5 years of age. Consequently, the next sections present pediatric oncology data utilizing the PedsQL™ (Pediatric Quality of Life Inventory™) that includes child self-report for ages 5–18 years and parent proxy-report for ages 2–18 years to illustrate the feasibility of using HRQOL measures across this broader age range for child and parent reports. These data include substantially larger sample sizes than the pediatric oncology studies published in the *Journal of Pediatric Psychology* during the past 5 years.

### PedsQL™ Measurement Model

Consistent with the measurement paradigm that generic and disease-specific HRQOL measures should be

administered so as to gain a more comprehensive evaluation of the patient’s HRQOL, the PedsQL™ Measurement Model was designed as a modular approach to measuring pediatric HRQOL, developed to integrate the relative merits of generic and disease-specific approaches (Varni et al., 1999). An explicit goal of the PedsQL™ Measurement Model was to develop and test brief measures for the broadest age group empirically feasible, specifically including child self-report for the youngest children possible (Varni, Limbers, & Burwinkle, 2007a). Thus, the PedsQL™ Measurement Model emphasizes the child’s perceptions. The PedsQL™ includes child self-report for ages 5–18 and parent proxy-report for ages 2–18 years (Varni, Burwinkle, Seid, & Skarr, 2003; Varni, Seid, & Kurtin, 2001). For ages 8–18 years, the PedsQL™ is self-administered. For ages 5–7 years, the PedsQL™ is interviewer-administered.

The PedsQL™ 4.0 Generic Core Scales were designed for application in both healthy and patient populations (Varni, Burwinkle, & Seid, 2006; Varni et al., 2001, 2003), while the PedsQL™ modules for pediatric oncology were designed to measure HRQOL dimensions specifically tailored for pediatric patients with cancer (Palmer et al., 2007; Varni, Burwinkle, Katz, Meeske, & Dickinson, 2002).

Tables III and IV illustrate composite published data utilizing the PedsQL™ 4.0 Generic Core Scales and PedsQL™ Multidimensional Fatigue Scale for samples of healthy children and pediatric oncology patients,

**Table III.** Scale Descriptives for PedsQL™ 4.0 Generic Core Scales Child Self-Report and Parent Proxy-Report in Oncology Sample and Comparisons with Healthy Children Scores

Scale	Number of Items	Oncology sample			Healthy sample			Difference	Effect size	t
		n	Mean	SD	n	Mean	SD			
Child self-report										
Total score	23	389	71.90	16.14	5480	83.84	12.65	11.94	0.94	17.62***
Physical health	8	389	71.98	21.39	5470	87.53	13.50	15.55	1.15	20.94***
Psychosocial health	15	389	72.00	16.32	5469	81.87	14.09	9.87	0.70	13.19***
Emotional functioning	5	389	72.04	20.86	5468	79.33	18.15	7.29	0.40	7.58***
Social functioning	5	389	75.38	21.11	5455	85.15	16.76	9.77	0.58	10.90***
School functioning	5	354	68.24	19.62	5412	81.12	16.45	12.88	0.78	14.08***
Parent proxy-report										
Total score	23	557	68.42	19.22	9430	82.70	15.40	14.28	0.93	20.83***
Physical health	8	557	67.49	25.09	9413	84.48	19.51	16.99	0.87	19.50***
Psychosocial health	15	557	69.09	18.43	9431	81.65	15.22	12.56	0.83	18.57***
Emotional functioning	5	557	67.47	20.70	9410	81.31	16.50	13.84	0.84	18.89***
Social functioning	5	556	72.80	22.31	9406	83.70	19.43	10.90	0.56	12.62***
School functioning	5	428	66.27	23.15	7898	78.83	19.59	12.56	0.64	12.71***

Higher values equal better health-related quality of life. Effect sizes are designated as small (0.20), medium (0.50), and large (0.80). Oncology sample was derived from Varni et al. (2002), Palmer et al. (2007), and Bhat et al. (2005). Healthy sample was derived from Varni et al. (2001, 2003).

\*\*\*p < .001.

**Table IV.** Scale Descriptives for PedsQL™ Multidimensional Fatigue Scale Child Self-Report and Parent Proxy-Report in Oncology Sample and Comparisons with Healthy Children Scores

Scale	Number of items	Oncology sample			Healthy sample			Difference	Effect size	<i>t</i>
		<i>n</i>	Mean	<i>SD</i>	<i>n</i>	Mean	<i>SD</i>			
Child self-report										
Total fatigue	18	275	69.92	18.19	52	80.49	13.33	10.57	0.79	-3.99***
General fatigue	6	275	73.99	19.28	52	85.34	14.95	11.35	0.76	-4.02***
Sleep/rest fatigue	6	275	66.24	22.79	52	75.00	18.76	8.76	0.47	-2.61**
Cognitive fatigue	6	275	69.54	22.96	52	81.14	17.43	11.60	0.67	-3.46**
Parent proxy-report										
Total fatigue	18	436	74.34	18.74	102	89.63	11.38	15.29	1.34	-7.90***
General fatigue	6	436	71.73	22.47	102	89.30	13.33	17.57	1.32	-7.59***
Sleep/rest fatigue	6	436	74.52	21.70	102	88.86	14.72	14.34	0.97	-6.34***
Cognitive fatigue	6	436	76.75	23.57	102	90.72	15.15	13.97	0.92	-5.72***

Higher values equal better health-related quality of life. Effect sizes are designated as small (0.20), medium (0.50), and large (0.80). Oncology sample was derived from Varni et al. (2002) and Palmer et al. (2007). Healthy sample was derived from Varni et al. (2002).

\*\**p* < .01, \*\*\**p* < .001.

**Table V.** PedsQL™ 4.0 Generic Core Scales and PedsQL™ Multidimensional Fatigue Scale Internal Consistency Reliability for Child Self-Report and Parent Proxy-Report Total Scale Score by Age in Oncology Sample

Scale	Age group (years)				
	Toddler (2–4)	Young child (5–7)	Child (8–12)	Adolescent (13–18)	Total sample
Child self-report					
Total score generic core	NA	.81 ( <i>n</i> = 80)	.87 ( <i>n</i> = 151)	.91 ( <i>n</i> = 118)	.87 ( <i>n</i> = 349)
Total score fatigue	NA	.86 ( <i>n</i> = 73)	.88 ( <i>n</i> = 112)	.92 ( <i>n</i> = 87)	.89 ( <i>n</i> = 272)
Parent proxy-report					
Total score generic core	.90 ( <i>n</i> = 116)	.92 ( <i>n</i> = 126)	.92 ( <i>n</i> = 173)	.94 ( <i>n</i> = 135)	.93 ( <i>n</i> = 550)
Total score fatigue	.89 ( <i>n</i> = 102)	.91 ( <i>n</i> = 106)	.93 ( <i>n</i> = 126)	.95 ( <i>n</i> = 96)	.93 ( <i>n</i> = 430)

NA, not applicable.

Data derived from Varni et al. (2002), Palmer et al. (2007), and Bhat et al. (2005).

demonstrating significant and large differences between the oncology sample and the healthy sample across HRQOL dimensions. Table V demonstrates internal consistency reliability of the Total Scale Scores for the Generic Core and Fatigue Scales. These data illustrate an approach in which both child self-report and parent proxy-report reliability and validity are demonstrated with parallel instruments, enabling comparisons within pediatric clinical trials from these two perspectives on child HRQOL.

### Clinically Important Difference

The minimal clinically important difference (MCID) has been defined as the smallest difference in a score of a domain of interest that patients perceive to be beneficial and that would mandate, in the absence of troublesome side effects and excessive costs, a change in the patient's management (Jaeschke, Singer, & Guyatt, 1989). The standard error of measurement (SEM) (Wyrwich, Tierney, & Wolinsky, 1999) has been linked to the MCID, in which

one SEM identified the MCID in responsiveness in a HRQOL measure (Wyrwich, Tierney, & Wolinsky, 2002). Thus, excellent agreement between the SEM and MCID has been shown (Wyrwich et al., 2002). As an illustration, the MCID for the PedsQL™ 4.0 Scale Scores has been determined through calculating the SEM. A 4.4 change in the PedsQL™ 4.0 Total Scale Score for child self-report has been determined as a minimal clinically meaningful difference, while a 4.5 change in PedsQL™ 4.0 Total Scale Score for parent proxy-report was determined as a minimal clinically meaningful difference (Varni et al., 2003). Thus, the MCID can provide a metric for determining meaningful change in a clinical trial, or in the planning stages of a clinical trial in order to determine the sample size needed to detect a meaningful clinical difference.

### Cut-Point for At-Risk Status

Scores approximating one standard deviation below the population mean have been proposed as a meaningful cut-off point score for an at-risk status for impaired HRQOL



relative to population means (Matza et al., 2004; Varni et al., 2005). As an illustration, cut-off points for at-risk status for impaired HRQOL have been examined for the PedsQL™ 4.0 using the one standard deviation below the mean of the total population sample (Varni et al., 2003). For child self-report, the PedsQL™ 4.0 Total Scale Score cut-off point score was shown to be 69.7 (parent proxy-report score of 65.4). In order to provide a clinical context for these cut-off scores, it is useful to examine Total Scale Scores for children with physician-diagnosed chronic health conditions. For example, children with newly diagnosed cancer on-treatment self-report a PedsQL™ 4.0 Total Scale Score of 68.9 (parent proxy-report score of 67.0) (Varni et al., 2002), approximating the proposed cut-off scores for impaired HRQOL.

### **Differences between HRQOL and At-The-Moment Assessment**

Developments in ecological momentary assessment (EMA) suggest the benefits of measuring symptoms at-the-moment in ecologically relevant environments (Stone & Shiffman, 1994). The measurement of present or at-the-moment functioning has been well established for pediatric pain intensity for several decades (McGrath, 1990; Varni & Bernstein, 1991).

Typically, HRQOL instruments measure functioning retrospectively over the past 7 days or the past 1 month. In contrast, at-the-moment instruments measure symptoms as they occur; utilizing paper-and-pencil or electronic data capture modalities. EMA research with adult patients demonstrates the utility of at-the-moment assessment in disentangling the interrelationships between such diverse constructs as pain, mood, fatigue, coping, and social support through a daily process analysis (Feldman, Downey, & Schaffer-Neitz, 1999). The application of these methods and technologies to the pediatric population will require measurement instruments that are developmentally appropriate for young children as well as older children and teens. Additionally, similar to research with adult cancer patients (Banthia et al., 2006), the correspondence between daily measures and weekly or monthly measures needs to be investigated.

### **The Importance of Child Self-Report for Ages 5–7 Years: An Empirical Illustration**

A recent clinical trial in pediatric cancer illustrates the importance of attaining child self-report for the youngest children empirically feasible. This double-blind, placebo-controlled study evaluated the effects of once-weekly

epoetin alfa (EPO) on the HRQOL of anemic pediatric cancer patients 5–18 years of age receiving myelosuppressive chemotherapy in a national multisite randomized controlled clinical trial using the PedsQL™ 4.0 as the HRQOL outcome measure (Razzouk et al., 2006). Mean patient-reported PedsQL™ 4.0 Total Scale Score at the final visit was significantly greater in the EPO group among patients of ages 5–7 years (88.0 vs. 78.1,  $p = .043$ ), but not among those aged 8–18 years. These HRQOL findings are consistent with the hemoglobin (Hb) data, in which among patients aged 5–7 years, 92% in the EPO group and 41.2% in the placebo group were Hb responders. The largest disparity in Hb response rate between EPO and placebo control groups was in children of age 5–7 years (Hinds et al., 2005), supporting the HRQOL differences between treatment groups demonstrated by this age group. Additionally, a post hoc analysis of the correlations between Hb and HRQOL identified a significant correlation between change in Hb from baseline to the final visit in the PedsQL™ Total Scale Score in the EPO group, but not in the placebo group based on patient self-report (Razzouk et al., 2006). Notably, there were no significant differences detected by parent proxy-report. Taken together, these data support the importance of patient self-report in pediatric oncology clinical trials when HRQOL is designated as a health outcome. In other words, “some treatment effects are known only to the patient” (FDA, 2006).

### **Conclusions**

Evidence now available demonstrates that pediatric patients aged 5–18 years can reliably and validly self-report their HRQOL when an age-appropriate measurement instrument is utilized. Pediatric PROs should be considered as the standard for HRQOL measurement in pediatric oncology clinical trials and research in which patient HRQOL is investigated. In this way, the voices of the children will be heard in matters pertaining to their health and well-being. Parent proxy-report should also be considered as complementary, since parents’ perceptions of their child HRQOL often drives health care utilization, and further provides the opportunity for HRQOL measurement when pediatric patients are unable or unwilling to provide self-report.

### **Acknowledgment**

J.W.V. holds the copyright and the trademark for the PedsQL™ and receives financial compensation from the Mapi Research Trust, which is a nonprofit research institute that charges distribution fees to for-profit

companies that use the Pediatric Quality of Life Inventory™.

*Conflict of interest:* None declared.

Received August 31, 2006; revisions received January 17, 2007; accepted January 26, 2007

## References

- Achenbach, T. M., McConaughy, S. H., & Howell, C. T. (1987). Child/adolescent behavioral and emotional problems: Implications of cross-informant correlations for situational specificity. *Psychological Bulletin*, *101*, 213–232.
- Acquadro, C., Berzon, R., Dubois, D., Leidy, N. K., Marquis, P., Revicki, D., et al. (2003). Incorporating the patient's perspective into drug development and communication: An ad hoc task force report of the patient-reported outcomes (PRO) harmonization group meeting at the Food and Drug Administration, February 16, 2001. *Value in Health*, *6*, 522–531.
- Banthia, R., Malcarne, V. L., Roesch, S. C., Ko, C. M., Greensbergs, H. L., Varni, J. W., et al. (2006). Correspondence between daily and weekly fatigue reports in breast cancer survivors. *Journal of Behavioral Medicine*, *29*, 269–279.
- Barakat, L. P., Alderfer, M. A., & Kazak, A. E. (2006). Posttraumatic growth in adolescent survivors of cancer and their mothers and fathers. *Journal of Pediatric Psychology*, *31*, 413–419.
- Barakat, L. P., Hetzke, J. D., Foley, B., Carey, M. E., Gyato, K., & Phillips, P. C. (2003). Evaluation of a social-skills training group intervention with children treated for brain tumors: A pilot study. *Journal of Pediatric Psychology*, *28*, 299–307.
- Berg-Nielsen, T. S., Vika, A., & Dahl, A. A. (2003). When adolescents disagree with their mothers: CBCL-YSR discrepancies related to maternal depression and adolescent self-esteem. *Child: Care, Health and Development*, *29*, 207–213.
- Bhat, S. R., Goodwin, T. L., Burwinkle, T. M., Lansdale, M. F., Dahl, G. V., Huhn, S. L., Gibbs, I. C., Donaldson, S. S., Rosenblum, R. K., Varni, J. W., & Fisher, P. G. (2005). Profile of daily life in children with brain tumors: An assessment of health-related quality of life. *Journal of Clinical Oncology*, *23*, 5493–5500.
- Campo, J. V., Comer, D. M., Jansen-McWilliams, L., Gardner, W., & Kelleher, K. J. (2002). Recurrent pain, emotional distress, and health service use in childhood. *Journal of Pediatrics*, *141*, 76–83.
- Chang, P., & Yeh, C. (2005). Agreement between child self-report and parent proxy-report to evaluate quality of life in children with cancer. *Psycho-Oncology*, *14*, 125–134.
- Clancy, C., McGrath, P., & Oddson, B. (2005). Pain in children and adolescents with spina bifida. *Developmental Medicine and Child Neurology*, *47*, 27–34.
- Clarke, S. A., & Eiser, C. (2004). The measurement of health-related quality of life in pediatric clinical trials: A systematic review. *Health and Quality of Life Outcomes*, *2*, 1–5.
- Creameens, J., Eiser, C., & Blades, M. (2006a). Characteristics of health-related self-report measures for children aged three to eight years: A review of the literature. *Quality of Life Research*, *15*, 739–754.
- Creameens, J., Eiser, C., & Blades, M. (2006b). Factors influencing agreement between child self-report and parent proxy-reports on the Pediatric Quality of Life Inventory™ 4.0 (PedsQL™) Generic Core Scales. *Health and Quality of Life Outcomes*, *4*, 1–8.
- Dahlquist, L. M., & Pendley, J. S. (2005). When distraction fails: Parental anxiety and children's responses to distraction during cancer procedures. *Journal of Pediatric Psychology*, *30*, 623–628.
- De Clercq, B., De Fruyt, F., Koot, H. M., & Benoit, Y. (2004). Quality of life in children surviving cancer: A personality and multi-informant perspective. *Journal of Pediatric Psychology*, *29*, 579–590.
- De Los Reyes, A., & Kazdin, A. E. (2004). Measuring informant discrepancies in clinical child research. *Psychological Assessment*, *16*, 330–334.
- Drotar, D., Schwartz, L., Palermo, T. M., & Burant, C. (2006). Factor structure of the Child Health Questionnaire-Parent Form in pediatric populations. *Journal of Pediatric Psychology*, *31*, 127–138.
- Eiser, C. (2004). Use of quality of life measures in clinical trials. *Ambulatory Pediatrics*, *4*, 395–399.
- Eiser, C., & Morse, R. (2001). Can parents rate their child's health-related quality of life?: Results from a systematic review. *Quality of Life Research*, *10*, 347–357.
- FDA. (2006). *Guidance for Industry: Patient-reported outcome measures: Use in medical product development to support labeling claims*. Rockville, MD: Center for

- Drug Evaluation and Research, Food and Drug Administration.
- Felder-Puig, R., diGallo, A., Waldenmair, M., Norden, P., Winter, A., Gadner, H., et al. (2006). Health-related quality of life of pediatric patients receiving allogeneic stem cell or bone marrow transplantation: Results of a longitudinal, multi-center study. *Bone Marrow Transplantation*, 38, 119–126.
- Feldman, S. I., Downey, G., & Schaffer-Neitz, R. (1999). Pain, negative mood, and perceived support in chronic pain patients: A daily diary study of people with reflex sympathetic dystrophy syndrome. *Journal of Consulting and Clinical Psychology*, 67, 776–785.
- Hays, R. M., Valentine, J., Haynes, G., Geyer, J. R., Villareale, N., McKinstry, B., et al. (2006). The Seattle Pediatric Palliative Care Project: Effects on family satisfaction and health-related quality of life. *Journal of Palliative Medicine*, 9, 716–728.
- Helton, S. C., Corwyn, R. F., Bonner, M. J., Brown, R. T., & Mulhern, R. K. (2006). Factor analysis and validity of the Conners Parent and Teacher Rating Scales in childhood cancer survivors. *Journal of Pediatric Psychology*, 31, 200–208.
- Hinds, R. S., Hockenberry, M., Feusner, J., Hord, J. D., Rackoff, W., & Rozzouk, B. J. (2005). Hemoglobin response and improvements in quality of life in anemic children with cancer receiving myelosuppressive chemotherapy. *Journal of Supportive Oncology*, 3 (Suppl 4), 10–11.
- Jaeschke, R., Singer, J., & Guyatt, G. H. (1989). Measurement of health status: Ascertaining the minimal clinically important difference. *Controlled Clinical Trials*, 10, 407–415.
- Janicke, D. M., Finney, J. W., & Riley, A. W. (2001). Children's health care use: A prospective investigation of factors related to care-seeking. *Medical Care*, 39, 990–1001.
- Johnston, C. A., Steele, R. G., Herrera, E. A., & Phipps, S. (2003). Parent and child reporting of negative life events: Discrepancy and agreement across pediatric samples. *Journal of Pediatric Psychology*, 28, 579–588.
- Klosky, J. L., Tyc, V. L., Srivastava, D. K., Tong, X., Kronenberg, M., Booker, Z. J., et al. (2004). Brief report: Evaluation of an interactive intervention designed to reduce pediatric distress during radiation therapy procedures. *Journal of Pediatric Psychology*, 29, 621–626.
- Levi, R. B., & Drotar, D. (1999). Health-related quality of life in childhood cancer: Discrepancy in parent-child reports. *International Journal of Cancer*, 12, 58–64.
- Matza, L. S., Swensen, A. R., Flood, E. M., Secnik, K., & Leidy, N. K. (2004). Assessment of health-related quality of life in children: A review of conceptual, methodological, and regulatory issues. *Value in Health*, 7, 79–92.
- McGrath, P. A. (1990). *Pain in children: Nature, assessment, and treatment*. New York: Guilford.
- Mulhern, R. K., Ochs, J., Armstrong, D., Horowitz, M., Friedman, A., Copeland, D., et al. (1989). Assessment of quality of life among pediatric patients with cancer. *Psychological Assessment*, 1, 130–138.
- Nathan, P. C., Furlong, W., & Barr, R. D. (2004). Challenges to the measurement of health-related quality of life in children receiving cancer therapy. *Pediatric Blood and Cancer*, 43, 215–223.
- Palmer, S. N., Meeske, K. A., Katz, E. R., Burwinkle, T. M., & Varni, J. W. (in press). The PedsQL™ Brain Tumor Module: Initial reliability and validity. *Pediatric Blood and Cancer*.
- Parsons, S. K., Shih, M., DuHamel, K. N., Ostroff, J., Mayer, D. K., Austin, J., et al. (2006). Maternal perspectives on children's health-related quality of life during the first year after pediatric hematopoietic stem cell transplant. *Journal of Pediatric Psychology*, 31, 1100–1115.
- Patrick, D. L., & Deyo, R. A. (1989). Generic and disease-specific measures in assessing health status and quality of life. *Medical Care*, 27, S217–S233.
- Phipps, S., Larson, S., Long, A., & Rai, S. N. (2006). Adaptive style and symptoms of posttraumatic stress in children with cancer and their parents. *Journal of Pediatric Psychology*, 31, 298–309.
- Razzouk, B. I., Hord, J. D., Hockenberry, M., Hinds, P. S., Feusner, J., Williams, D., et al. (2006). Double-blind, placebo-controlled study of quality of life, hematologic end points, and safety of weekly epoetin alfa in children with cancer receiving myelosuppressive chemotherapy. *Journal of Clinical Oncology*, 24, 3583–3589.
- Reeves, C. B., Palmer, S. L., Reddick, W. E., Merchant, T. E., Buchanan, G. M., Gajjar, A., et al. (2006). Attention and memory functioning among pediatric patients with medulloblastoma. *Journal of Pediatric Psychology*, 31, 272–280.
- Richters, J. E. (1992). Depressed mothers as informants about their children: A critical review of the

- evidence for distortion. *Psychological Bulletin*, 112, 485–499.
- Russell, K. M. W., Hudson, M., Long, A., & Phipps, S. (2006). Assessment of health-related quality of life in children with cancer: Consistency and agreement between parent and child reports. *Cancer*, 106, 2267–2274.
- Schwartz, L., & Drotar, D. (2006). Posttraumatic stress and related impairment in survivors of childhood cancer in early adulthood compared to healthy peers. *Journal of Pediatric Psychology*, 31, 356–366.
- Sherman, S. A., Eisen, S., Burwinkle, T. M., & Varni, J. W. (2006). The PedsQL™ Present Functioning Visual Analogue Scales: Preliminary reliability and validity. *Health and Quality of Life Outcomes*, 4, 1–10.
- Sprangers, M. A. G., & Aaronson, N. K. (1992). The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: A review. *Journal of Clinical Epidemiology*, 45, 743–760.
- Sprangers, M. A. G., Cull, A., Bjordal, K., Groenvold, M., & Aaronson, N. K. (1993). The European organization for research and treatment of cancer approach to quality of life assessment: Guidelines for developing questionnaire modules. *Quality of Life Research*, 2, 287–295.
- Steele, R. G., Dreyer, M. L., & Phipps, S. (2004). Patterns of maternal distress among children with cancer and their association with child emotional and somatic distress. *Journal of Pediatric Psychology*, 29, 507–517.
- Stone, A. A., & Shiffman, S. (1994). Ecological momentary assessment (EMA) in behavioral medicine. *Annals of Behavioral Medicine*, 16, 199–202.
- Stoppelbein, L. A., Greening, L., & Elkin, T. D. (2006). Risk of posttraumatic stress symptoms: A comparison of child survivors of pediatric cancer and parental bereavement. *Journal of Pediatric Psychology*, 31, 367–376.
- Theunissen, N. C. M., Vogels, T. G. C., Koopman, H. M., Verrips, G. H. W., Zwinderman, K. A. H., Verloove-Vanhorick, S. P., et al. (1998). The proxy problem: Child report versus parent report in health-related quality of life research. *Quality of Life Research*, 7, 387–397.
- Tyc, V. L., Lensing, S., Klosky, J., Rai, S. N., & Robinson, L. (2005). A comparison of tobacco-related risk factors between adolescents with and without cancer. *Journal of Pediatric Psychology*, 30, 359–370.
- Vance, Y. H., Morse, R. C., Jenney, M. E., & Eiser, C. (2001). Issues in measuring quality of life in childhood cancer: Measures, proxies, and parental mental health. *Journal of Child Psychology and Psychiatry*, 42, 661–667.
- Varni, J. W., & Bernstein, B. H. (1991). Evaluation and management of pain in children with rheumatic diseases. *Rheumatic Disease Clinics of North America*, 17, 985–1000.
- Varni, J. W., Burwinkle, T. M., Katz, E. R., Meeske, K., & Dickinson, P. (2002). The PedsQL™ in pediatric cancer: Reliability and validity of the Pediatric Quality of Life Inventory™ Generic Core Scales, multidimensional fatigue scale, and cancer module. *Cancer*, 94, 2090–2106.
- Varni, J. W., Burwinkle, T. M., & Lane, M. M. (2005). Health-related quality of life measurement in pediatric clinical practice: An appraisal and precept for future research and application. *Health and Quality of Life Outcomes*, 34, 1–9.
- Varni, J. W., Burwinkle, T. M., & Seid, M. (2006). The PedsQL™ 4.0 as a school population health measure: Feasibility, reliability, and validity. *Quality of Life Research*, 15, 203–215.
- Varni, J. W., Burwinkle, T. M., Seid, M., & Skarr, D. (2003). The PedsQL™ 4.0 as a pediatric population health measure: Feasibility, reliability, and validity. *Ambulatory Pediatrics*, 3, 329–341.
- Varni, J. W., Katz, E. R., Colegrove, R., & Dolgin, M. (1995). Adjustment of children with newly diagnosed cancer: Cross-informant variance. *Journal of Psychosocial Oncology*, 13, 23–38.
- Varni, J. W., Katz, E. R., Seid, M., Quiggins, D. J. L., Friedman-Bender, A., & Castro, C. M. (1998). The Pediatric Cancer Quality of Life Inventory (PCQL): I. Instrument development, descriptive statistics, and cross-informant variance. *Journal of Behavioral Medicine*, 21, 179–204.
- Varni, J. W., Limbers, C. A., & Burwinkle, T. M. (2007a). How young can children reliably and validly self-report their health-related quality of life?: An analysis of 8,591 children across age subgroups with the PedsQL™ 4.0 Generic Core Scales. *Health and Quality of Life Outcomes*, 5, 1–13.
- Varni, J. W., Limbers, C. A., & Burwinkle, T. M. (2007b). Parent proxy-report of their children's health-related quality of life: An analysis of 13,878 parents' reliability and validity across age subgroups using the PedsQL™ 4.0 Generic Core Scales. *Health and Quality of Life Outcomes*, 5, 1–10.

- Varni, J. W., Seid, M., & Kurtin, P. S. (2001). PedsQL™ 4.0: Reliability and validity of the Pediatric Quality of Life Inventory™ Version 4.0 Generic Core Scales in healthy and patient populations. *Medical Care*, 39, 800–812.
- Varni, J. W., Seid, M., & Rode, C. A. (1999). The PedsQL™: Measurement model for the Pediatric Quality of Life Inventory. *Medical Care*, 37, 126–139.
- Varni, J. W., & Setoguchi, Y. (1992). Screening for behavioral and emotional problems in children and adolescents with congenital or acquired limb deficiencies. *American Journal of Diseases of Children*, 146, 103–107.
- Varni, J. W., Thompson, K. L., & Hanson, V. (1987). The Varni/Thompson Pediatric Pain Questionnaire: I. Chronic musculoskeletal pain in juvenile rheumatoid arthritis. *Pain*, 28, 27–38.
- Willke, R. J., Burke, L. B., & Erickson, P. (2004). Measuring treatment impact: A review of patient-reported outcomes and other efficacy endpoints in approved product labels. *Controlled Clinical Trials*, 25, 535–552.
- World Health Organization. (1948). *Constitution of the World Health Organization: Basic document*. Geneva, Switzerland: World Health Organization.
- Wyrwich, K., Tierney, W., & Wolinsky, F. (1999). Further evidence supporting an SEM-based criterion for identifying meaningful intra-individual changes in health-related quality of life. *Journal of Clinical Epidemiology*, 52, 861–873.
- Wyrwich, K., Tierney, W., & Wolinsky, F. (2002). Using the standard error of measurement to identify important changes on the Asthma Quality of Life Questionnaire. *Quality of Life Research*, 11, 1–7.
- Yeh, C. H., Chang, C. W., & Chang, P. C. (2005). Evaluating quality of life in children with cancer using children's self-reports and parent-proxy reports. *Nursing Research*, 54, 354–362.