

Article

# From the Child's Word to Clinical Intervention: Novel, New, and Innovative Approaches to Symptoms in Pediatric Palliative Care

Katharine E. Brock <sup>1,2,3</sup> , Joanne Wolfe <sup>4,5</sup> and Christina Ullrich <sup>4,5,\*</sup>

<sup>1</sup> Aflac Cancer and Blood Disorders Center of Children's Healthcare of Atlanta, Atlanta, GA 30322, USA; Katharine.brock@choa.org

<sup>2</sup> Pediatric Palliative Care, Children's Healthcare of Atlanta, Atlanta, GA 30322, USA

<sup>3</sup> Department of Pediatrics, Division of Pediatric Hematology/Oncology, Emory University, Atlanta, GA 30322, USA

<sup>4</sup> Department of Psychosocial Oncology and Palliative Care, Dana-Farber Cancer Institute, Boston, MA 02215, USA; Joanne\_Wolfe@dfci.harvard.edu

<sup>5</sup> Department of Pediatric Hematology/Oncology, Dana-Farber Cancer Institute, Boston Children's Hospital Cancer and Blood Disorders Center, Boston, MA 02215, USA

\* Correspondence: Christina\_Ullrich@dfci.harvard.edu; Tel.: +1-617-632-4997

Received: 19 December 2017 Accepted: 21 March 2018; Published: 28 March 2018



**Abstract:** Despite vast improvements in disease-based treatments, many children live with life-threatening disorders that cause distressing symptoms. These symptoms can be difficult to comprehensively assess and manage. Yet, frequent and accurate symptom reporting and expert treatment is critical to preserving a patient's physical, psychological, emotional, social, and existential health. We describe emerging methods of symptom and health-related quality-of-life (HRQOL) assessment through patient-reported outcomes (PROs) tools now used in clinical practice and novel research studies. Computer-based and mobile apps can facilitate assessment of symptoms and HRQOL. These technologies can be used alone or combined with therapeutic strategies to improve symptoms and coping skills. We review technological advancements, including mobile apps and toys, that allow improved symptom reporting and management. Lastly, we explore the value of a pediatric palliative care interdisciplinary team and their role in assessing and managing distressing symptoms and minimizing suffering in both the child and family. These methods and tools highlight the way that novel, new, and innovative approaches to symptom assessment and management are changing the way that pediatrics and pediatric palliative care will be practiced in the future.

**Keywords:** pediatric palliative care; quality of life; symptom management; hospice; patient-reported outcomes; mobile apps

## 1. Introduction

Over 400,000 US children live with life-threatening or chronic, complex conditions [1,2]. Over 12,400 children are diagnosed with cancer annually in the United States [3]. Despite vast improvement in overall survival, less attention has been focused on comprehensively assessing and treating symptoms. Even with a bevy of new cancer-directed therapies, children continue to suffer from distressing symptoms such as pain, fatigue, nausea/vomiting, decreased appetite, anxiety, and depression [4–6]. Symptoms may arise from the disease itself, or commonly from the treatments prescribed. Many of the symptoms children suffer through are experienced in the home setting, away from the hospital, contributing to the perception of few treatment options [7]. Numerous factors lead to poor symptom control at the patient, parent, healthcare team, and system levels [8]. These include

a lack of provider time and skill in addressing symptoms, infrequent use of systematic assessment tools, and provider uncertainty around the accuracy of pediatric patient-reported symptoms [8,9]. Patient forgetfulness, the desire to be a “good patient”, and the belief that one needs to experience symptoms for better chance of cure also impact symptom reporting [10,11]. System challenges include lack of sufficient integrative medicine, chronic pain, psychiatry, psychology, and palliative care resources to meet patients’ needs [12–14]. Multiple interventions have been attempted to improve the reporting of symptoms by patients and families, such as improved outpatient screening [15], frequent monitoring [8,16,17], increased use of patient-reported outcomes (PROs) [5,18], technological advances [8,16,17], and embedding palliative care experts within oncology centers [19]. In this article, we describe the current state of symptom assessment and management within pediatric palliative care, with a focus on pediatric oncology. We also describe emerging and novel approaches to symptom assessment for patients with serious and complex illness.

## 2. Technological Advances for Symptom Assessment, Reporting, and Management

Technology use in America is ubiquitous. Ninety-five percent of Americans own a cellphone [20]; 70% own a smartphone, up from 35% in 2011 [20]. Of US adults aged 18–29 years, 100% own a cellphone, with 92% owning a smartphone [20]; among 12–17 year-olds, nearly three-quarters own a smartphone [21]. Along with mobile phones, Americans own a range of other devices; nearly 80% of US adults own a computer, and 51% own tablet devices [20]. Roughly three-quarters have internet access in the home [22]. Of teens and adults ages 18–29 years, nearly 100% use the internet regularly [21,22], and 71–86% are social media users, often accessing sites daily [21,23]. Notably, the use of these devices has extended into the healthcare setting. Technology has changed how patients and clinicians communicate with each other outside of the hospital and how patients or parents connect with other families online. Patients utilize technology to remember appointments, instructions, and enhance their medication adherence [24,25].

As technology plays a larger role in children, patients, and families lives, hospitals, clinicians, and researchers have attempted to utilize technology for symptom assessment and integrate reports into the medical record. In technology’s most simple form, patients can be called or emailed symptom questionnaires to complete. This can be done while patients are in the hospital or waiting room, yet an important application is for longitudinal symptom tracking while patients are at home. Systems must be reliable, accurate, and permit efficient collection of symptom and health-related quality of life (HRQOL) data.

Electronic systems, usually employing a handheld computer and touch screen, are quite acceptable to patients [26–29]. While relatively little comparison of technology-based versus paper-based modes of administration has been conducted, one study found data equivalence between app-based and other delivery methods [30]. Another ( $n = 19$ ) study of children with or without a speech or voice disorder also found that the scores did not differ between paper and pencil and electronic handheld device groups. However, the percentage of children who made answering errors or omissions was significantly smaller in the group who used an electronic handheld device. The device also permitted more efficient collection and manipulation of data [31].

Increasing in complexity, survey results can be fed back to the research team and physician in real time. Electronic methods of collecting data from patients have also allowed the presentation of real-time symptom and HRQOL measurements to clinicians, at the time of the clinical encounter with the patient. Feedback to clinicians is viewed favorably by patients [32,33] and clinicians alike [33]. Moreover, this strategy is feasible in busy oncology practices [34], does not increase consultation time, facilitates patient-clinician communication about symptoms or HRQOL, and increases the likelihood that symptom issues are addressed [33,35–38]. Many technology-based PRO collection systems permit assessment of symptoms and HRQOL in between clinic visits, at times that the clinician would not otherwise understand the patient’s condition. This is especially important since patients may be

unwilling to call the office, and routine PRO assessment may provide opportunities to attend to symptoms before they escalate.

### 3. Assessment of Child Symptoms and Health-Related Quality of Life

#### *The Science of Self and Proxy Reporting*

Accurate symptom reporting, timely assessment, and expert treatment are critical to preventing additional decrements to the patient’s physical, psychological, emotional, social, and existential domains of health. Child self-report is considered the gold standard for assessing symptom burden and HRQOL, as parents and clinicians tend to under-report the severity and number of symptoms children are experiencing [39,40]. Discrepancies among reporters have been demonstrated in several disease groups, including children with cancer, congenital cardiac disease, and those who are status-post bone marrow transplantation [41–43]; however, the direction of this association can vary. For example, parents of children with sickle cell disease have been shown to give worse ratings of their child’s HRQOL compared with the child’s ratings [44].

In general, concordance is better (informant discrepancy is less) with physical symptoms compared with psychological symptoms [45,46]. This difference was recently demonstrated to be true in a population of children who received a pediatric palliative care consult and may be explained by the fact that physical symptoms are more readily assessed based on biomedical or behavioral changes [47]. Parent ratings can also be affected by their own life experiences, mental state, and distress levels [43,45,48–50]. Considerations around use of child self-report versus parent or clinician proxy-report are summarized in Table 1. In the end, the best approach to differing perspectives is to take advantage of their diversity, incorporating all viewpoints to provide a more global picture of the child’s experience [43].

**Table 1.** Considerations around use of self, parent and clinician report when assessing child symptoms and health-related quality-of-life (HRQOL).

Self-Report	Parent Report	Clinician Report
<ul style="list-style-type: none"> <li>For subjective outcomes (e.g., symptoms, HRQOL), the person experiencing the outcomes is the expert. Thus, self-report is considered the gold standard</li> </ul>	<ul style="list-style-type: none"> <li>Parent often has a longstanding and nuanced knowledge of child; besides the child, is often considered “the expert” regarding the child’s experience</li> </ul>	<ul style="list-style-type: none"> <li>May or may not be familiar with child, which can impact ratings</li> </ul>
<ul style="list-style-type: none"> <li>Various factors (e.g., medical, developmental, cognitive) may influence self-report</li> </ul>	<ul style="list-style-type: none"> <li>When child unable to self-report, parent report is often considered the next best alternative</li> </ul>	<ul style="list-style-type: none"> <li>Valuable when the child cannot self-report due to developmental considerations or illness</li> </ul>
<ul style="list-style-type: none"> <li>Young and seriously ill children may be limited in their ability to self-report at all</li> </ul>	<ul style="list-style-type: none"> <li>In general, greater agreement with child ratings for observable functioning (e.g., physical symptoms and HRQOL) and less for functioning that cannot be observed (e.g., emotional symptoms and HRQOL)</li> </ul>	<ul style="list-style-type: none"> <li>Like all raters, reports may be colored by the rater’s own experiences, beliefs, skill level, academic interests, expectations and points of reference</li> </ul>
	<ul style="list-style-type: none"> <li>May be influenced by parent factors, such as parent anxiety or distress (generally associated with worse ratings) as well as parent expectations and points of reference</li> </ul>	<ul style="list-style-type: none"> <li>Clinicians may have the experience of caring for many children under similar circumstances, which can shape their views about a particular child’s experience</li> </ul>
	<ul style="list-style-type: none"> <li>Parent proxies can also provide input regarding the parent and family experience</li> </ul>	

Since child self-report is taken to be the gold standard when it comes to assessing their symptoms, novel methods are needed to obtain symptom assessments from children of all ages and developmental stages, validate additional pediatric measures across a wider variety of patient populations, understand patient-reported outcomes, translate results to the treating teams, and change supportive care therapies when warranted.

#### 4. Patient-Reported Outcomes Assessment

A patient-reported outcome (PRO) is “any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else” [51]. Medical outcomes have historically focused on biomedical or physiologic endpoints (e.g., progression free survival in oncology, overall survival). However, these outcomes do not capture a person’s experience of living with a medical condition or illness, such as side effects of the illness and its treatment, and treatment burden. To gain a better understanding of a patient’s lived experience, assessment of PRO that capture outcomes such as functional status, as well as aspects of HRQOL, including physical symptoms and functioning, emotional symptoms and social functioning are imperative. Adult oncologists endorse the utility of PRO collection, with clinical measures such as performance status being most important. PRO becomes even more important when multiple treatments options are under consideration, in the setting of advanced or incurable disease, or for patients receiving palliative care [52].

In recent years, systematic collection of PRO has also become an integral part of the assessment of new therapies and interventions [51,53]. Basch and colleagues demonstrated that patient self-reports of symptomatic adverse events (toxicities) were highly feasible (overall adherence of 93%) in a large, multicenter trial of 361 adults with cancer. Moreover, participants reported more toxicities than did investigators, indicating that this collection strategy utilizing PRO may enhance the precision of symptomatic toxicity collection in trials [54]. In both the clinical and research settings, PRO assessment is advantageous to patients, practitioners, and investigators alike, and therefore, integration of PRO assessment into clinical workflows and investigations will likely accelerate.

##### *Patient-Reported Outcomes Assessment with Feedback*

With regard to clinical outcomes, feedback of PRO to clinicians in the aforementioned study conducted by Basch and colleagues resulted in fewer emergency room visits and hospitalizations [55]. Feedback also resulted in improved survival [56]. Whether this was due to improved symptom control and mitigation/prevention of worsening toxicity or enhanced tolerance of continued treatment warrants additional study. PRO data can improve care delivered by informing patient and clinician expectations, catalyzing communication about important issues, and promoting shared decision-making such that interventions meeting a patient’s specific needs and goals are chosen. Recent experience with PRO reporting to clinicians in a large health care system also suggests that it enhances physician satisfaction and prevents burnout by enhancing physician-patient relationships, increasing workflow efficiency and enabling crucial conversations that otherwise may not occur [57]. Suggestions for PRO assessment and feedback to clinicians are presented in Table 3.

**Table 2.** Suggestions for use of patient-reported outcomes (PRO) and feedback reports in the clinical setting.

Aspects of Patient-Reported Outcomes and Feedback Reports	Considerations
Choice of measures and outcomes	Outcomes should be meaningful and important to the patient. When possible, select standardized measures. Utilize instruments that have been evaluated by members of the target audience. If available and pending context (research vs clinical), consider use of condition-specific measures which may be more sensitive to intervention effects. Carefully select frequency and timing of assessments to avoid survey fatigue, ensure that assessment points are clinically meaningful and provide results that can be acted upon in future clinical visits.

Table 2. Cont.

Aspects of Patient-Reported Outcomes and Feedback Reports	Considerations
Data presentation	Make displays intuitive using pie graphs and line charts showing trends in function and symptoms. Make reports easily accessible to viewers [58]. Present a defined, carefully selected set of data (avoid presenting too much). Present current scores and recent trends. Correlation of trends with recent clinical events (e.g., chemotherapy, hospitalization) is also helpful. Make scores easy to interpret for patients and clinicians. Provide context for clinicians who may not be familiar with symptom or HRQOL scores and meaningful changes in scores. Other strategies to effectively present results to patients and clinicians have recently been described [59,60].
Clinician Use	Make reports available at the point of care in electronic format via website, emailed to clinicians, and incorporated within the electronic medical record. The optimal mode will depend upon the clinical practice. Link reports to supportive care guidelines/recommendations for intervention Minimize disruption to the clinical workflow.
Implementation	Ensure buy-in from patients/families and clinicians alike when embarking on the study. Ensure patient interface is easy to use. Minimize time burden for all users. Ensure processes for responding to reports in a timely manner. Ensure adequate networks, software and properly configured devices for data collection.

## 5. Patient-Reported Outcomes in Pediatrics

Collection of PRO in pediatrics lags-behind the adult realm in both the clinical and research realm. For example, within the research realm, a review of clinical trials listed in ClinicalTrials.gov [61] and involving children with chronic conditions revealed that only 36 of 495 trials included patient and family-important outcomes, with these outcomes being particularly rare in drug trial and early phase trials [62]. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) is a well-established system by which adverse events are gleaned from the medical record, potentially missing subjective symptoms that are reported by the patient and not reliably contained in the medical record. The Pediatric Patient-Reported Outcomes version of the CTCAE, or PRO-CTCAE, builds on the established CTCAE, allowing the child's (or proxy's) voice to be a routine trial endpoint. While not yet publicly available, the hope is that through the Pediatric- and Proxy PRO-CTCAE measures, the impact of an investigational treatment on a child can be more fully understood and addressed [63,64]. This continues to be a research- and clinical trial-focused tool rather than for use in routine clinical care settings.

Regarding clinical use, pediatric oncologists report that routine assessment of PRO would be useful in their practice, particularly those focused on pain, feeling sad or depressed, overall physical symptoms, problems with therapy adherence, and emotional issues [65]. When PROs are collected frequently and routinely, the process is normalized. It conveys a message to patients and families that their perspectives and experiences are valued. This, of course, means that clinicians must respond to PRO collected data in the clinical setting so that child reports are not ignored.

### *Pediatric Patient-Reported Outcome Instrumentation*

Pediatric PRO collection has historically been challenged by the number of instruments developed for collection of PRO from children as well as their inconsistent use. Many of these instruments are not based on a similar conceptual foundation (i.e., instrument content and domains are founded on different conceptual frameworks). Pediatric PRO instruments have also been developed with the use of different psychometric methods and properties (e.g., cross-sectional versus longitudinal). As a result, a wide range of instruments exist, with varying degrees of reliability, validity, and comparability [66]. Recent systematic reviews assessing PROs for children with cancer confirmed that substantial

heterogeneity exists in content and distribution of items (e.g., which aspects of health are assessed and whether individual questions focus on function versus well-being) [67,68].

To address these issues, the National Institutes of Health (NIH)-sponsored PROMIS (Patient-Reported Outcomes Measurement Information System) measures, including pediatrics-specific measures, were developed in recent years as part of the NIH Roadmap for Medical Research Initiative [69–72]. Publicly available, PROMIS measures assess domains such as physical, emotional, and social health as well as symptoms (e.g., pain). PROMIS measures are designed to assess symptoms and function in the general population and in individuals living with chronic conditions with a brief completion time. Pediatric self-report PROMIS measures are available for ages 8–17 years and parent-proxy versions are available for children aged 5–17 years, in English, Spanish, and other languages. They are psychometrically sound, having undergone extensive testing using modern test theory, in both cross-sectional and longitudinal analyses (e.g., responsiveness, test-retest reliability) [73,74]. In addition, short forms and compatibility with computer adaptive testing make them highly usable. An additional strength of the PROMIS measures is that child and adult emotional distress measures are linked, allowing both populations to be evaluated within studies or for children to be followed into adulthood in longitudinal studies [75].

An innovative technological approach to instrumentation and collection of PRO is that of computer adaptive technology (CAT). In CAT, each question presented is selected based on a respondent's previous response. This permits generation of an accurate score based on fewer numbers of questions than standard item administration would require. Developed in Europe, the Kids-CAT system has been validated as a system for measuring physical and psychological well-being, parent relations, social support and peers, and school well-being in children with asthma, diabetes, or rheumatoid arthritis. In addition to providing greater measurement precision and lower test burden compared to conventional tests, it provides immediate feedback reports to clinicians [76–78].

## 6. Novel Tools, Apps, and Toys for Symptom Assessment and Management

### 6.1. Online or Computer-Based Tools

Online tools are being developed both in a research context, and also in a patient-focused manner. One example of a research-focused tool is PediQUEST [5]. Evaluated in the first randomized controlled trial of a supportive care intervention for children with advanced cancer, PediQUEST is a web-based PRO data collection system that prospectively and longitudinally collected child self-reported and parent proxy-reported symptoms and HRQOL at three large cancer centers [79]. The PediQUEST study demonstrated that collection of PRO from children with advanced cancer was highly feasible. For example, among 708 potential child administrations (i.e., assessments of children old enough to self-report), 98% were provided a report [80]. This is of particular importance given that child participants had advanced illness. When reports were sent to clinicians, both parents and clinicians valued the reports. Reports facilitated communication about symptoms and HRQOL and resulted in improved emotional symptoms and well-being [5].

KLIK (Kwaliteit van Leven In Kaart (Quality of Life in Clinical Practice) is another online tool for pediatric PRO reporting that was developed in the Netherlands, and evaluated in large studies with thousands of patients [81,82]. The KLIK website generates an e-mail several days before an appointment that allows children (8–18 years old) or parents (for children age 0–7 years old) to complete PRO measures [81]. KLIK transforms child responses into an eProfile which is shared with the child's health care provider via a central website [83]. In a randomized multicenter study of children with juvenile idiopathic arthritis, reports were reviewed during a routine appointment (intervention group). In this group, psychosocial topics were discussed more often, and clinicians were more satisfied with the care provided [82]. Similar studies in the pediatric oncology population also revealed that psychosocial issues were more frequently raised among those who received the reports, without increasing the duration of the clinical encounter [84,85]. Of note, participants were prompted

by email to complete assessments, suggesting that, at least in these pediatric populations, remote (i.e., not clinic-based) assessments are feasible.

Other online tools have been marketed in a direct to consumer fashion. My Quality (My Quality, Ltd., United Kingdom) is an online tool that allows families with children with life-limiting illness to designate and monitor parameters that they identify as impacting their quality of life [86]. Initial testing of the site revealed that it was highly usable and feasible, and the site's graphic representation of change over time facilitated collaboration in the child's care. Moreover, families who used the site had greater empowerment over time [87].

### 6.2. Mobile Apps

An increasing number of mobile apps designed for smart phones have also been developed for symptom tracking, symptom reporting, and symptom management, with some combining multiple focuses. Apps can be used by parents to report their young or non-verbal child's symptoms. Apps are particularly attractive for adolescent and young adults, who may not reliably report their symptoms in clinic, notably around sensitive topics such as sexual dysfunction or body image. Some apps are focused on one symptom, such as PainSquad+ for pain [16] or SyMon-SAYS for fatigue [8], while others such as Symple (Symple Health, Andover, United Kingdom) may assess a broader range of symptoms, including fatigue, nausea, and mental health issues [88]. Another smartphone app allows tracking of child pain and interference caused by pain while simultaneously tracking parent response to their pain. Such a strategy allows analysis of the inter-relationships between the child's pain experience and caregiver responses, such as how a child's pain and pain interference changes after a given type of caregiver responses (protective versus minimizing responses) and whether caregiver responses to pain is predicted by child factors, pain, or caregiver mood [89]. The validated measures utilized within these apps are varied, making it difficult to compare one to another. However, instituting app-based symptom tracking within a clinic or small group of providers is an area ripe for quality improvement research.

More advanced apps, such as Pain Buddy [17], are starting to couple assessment with analysis and targeted intervention. Instead of solely tracking symptoms and distress over time, apps now have the capability to generate reports, send alerts to physicians, and deliver a focused intervention to the user. This allows a physician to plan for pharmacologic therapies and the user to receive immediate non-pharmacologic treatment, including mindfulness or breathing techniques. Other publicly available apps designed for children and adolescents manage symptoms using non-pharmacologic therapies and by teaching coping skills for managing pain, symptoms, and stress [90]. Some examples are Healing Buddies Comfort Kit (Children's Hospitals and Clinics of Minnesota, Ridgeview Medical Center, and DesignWise Medical, Version 1.1, Minneapolis, MN, USA) [91], Mindfulness for Children (Mindfulness for Children, Version 1.2, Niva, Denmark) [92], and Positive Penguins [93] (HR INSIDE PTY LTD, Version 2.0, Melbourne, Australia).

### 6.3. Therapeutic Toys

One emerging area in pain management for children is the use of therapeutic toys. Toys are a fun incentive and can promote social, emotional, and intellectual development [94]. In medicine, toys and play have often been employed as a method of distraction during procedures, such as suturing or IV sticks, or to promote education, such as dolls to prepare children for port-a-cath or gastrostomy tube placement.

As toy technology advances, they can also be utilized as a therapeutic alternative, helping to reduce pain, stress, fear, and anxiety. Some hospitals are already utilizing advanced sensory rooms or machines which engage a patient's senses—smell, touch, sight, and sound. This can assist in having a calming effect and provide symptom relief without utilizing medication. Mixed-media toys may have both a physical toy and a mobile app that pairs with the toy to vibrate, feel emotions, and transport children to a soothing soundscape. One example is Jerry the Bear, a comforting

companion for children with type 1 diabetes (Sproutel, Inc, Version 1.2.0, Providence, RI, USA) [95]. Similar comforting companions and apps can be designed to entertain, comfort, educate, connect, and mimic a child’s experience.

While there are many limitations and practical challenges in using web-based mobile apps and toys to assess symptoms and improve a child’s quality of life, this is also an opportunity to involve patients and families in developing technology that is user-friendly. Children are incredibly creative and technology-savvy. Engaging children around the development of these programs, apps, and toys may empower them to take control over their symptoms by providing valuable perspectives on living through illness, hospitalizations, and procedures.

### 7. Meeting Patients Where They Are: Integration of Palliative Care in the Clinic Setting to Address Symptoms

Integration of palliative care principles and services into routine outpatient care for children with high-risk cancer disease is associated with improved symptom management for patients and quality of life (QOL) for both children and families [19,96–103]. Adult cancer centers have already demonstrated that integrating palliative care into the care of patients with cancer improved patient’s pain, fatigue, depression, anxiety, and sleep [104,105]. Currently, this model is becoming recognized in pediatrics [19,99,106]. Several oncology or palliative care clinics have integrated web-based, computerized symptom assessments and PROs with validated tools [107]. For example, the Memorial Symptoms Assessment Scale, Pediatric Quality of Life inventory, and PROMIS forms have been utilized in both a clinical context and in research studies [5,17].

Perhaps most importantly, an interdisciplinary team-based assessment of a patient and family often yields additional information that cannot be gleaned from a survey. While integration or embedding within specialty clinics, such as oncology or cardiology, can be difficult and logistically challenging, there is value to a specialty palliative care team assessing, treating, and following the patient and family over time [19,98]. While a physician, nurse practitioner or nurse is extremely valuable in symptom assessment and treatment, the perspective of other team members should not be discounted. In fact, it is the experience of many palliative care teams that the social worker, chaplain, psychologist, child life specialist, or clinical pharmacist can be incredibly beneficial in assessing and managing physical symptoms, psychological symptoms, spiritual distress, and psychosocial pain [108–111]. The rationale for this is that many discussions are not about the symptom itself, but the meaning behind the symptom. This can include uncertainty about the cause or the future and whether this means diminished function [112]. When a patient’s concern about a symptom is routed to a medical provider, a physician tends to give scientific medical responses, while the patient may desire a listening ear, reassurance and empathy. See Table 3 for an overview of the symptom assessment methods.

**Table 3.** Methods of pediatric symptom assessment.

Assessment	Strengths	Weaknesses	Application to PPC
Patient-reported outcomes (PROs)	<ul style="list-style-type: none"> <li>• Can be adapted to a number of electronic interfaces, including EMR and direct-to- clinician reports</li> <li>• Variety of choices for different symptoms, HRQOL measures</li> <li>• Valid and reliable measures for pediatric research studies</li> <li>• Can be fed back to clinical team for improved symptom management</li> </ul>	<ul style="list-style-type: none"> <li>• Long forms can be time-consuming</li> <li>• Need to consider child self-report vs. proxy report</li> <li>• PROs lacking for non-malignant conditions and within pediatric research</li> <li>• Limitation of PROs in patients at end-of life, or who are non-verbal</li> </ul>	<ul style="list-style-type: none"> <li>• Can be incorporated prior to and within symptom management visits</li> <li>• PROs can be completed at home, with hospice providers and sent to hospital-based team</li> <li>• Allows for multi-site research studies</li> </ul>

Table 3. Cont.

Assessment	Strengths	Weaknesses	Application to PPC
Online tools (e.g., KLIK, PediQUEST, MyQuality) [5,80,81,83,86]	<ul style="list-style-type: none"> <li>Utilize a variety of PROs</li> <li>Applicable in research and clinical settings</li> <li>Surveys prior to physician appointments increased psychosocial discussions</li> <li>Improves parent and clinician satisfaction</li> </ul>	<ul style="list-style-type: none"> <li>Initial investment into development and technology</li> <li>Need for interface between electronic assessments and EMR</li> </ul>	<ul style="list-style-type: none"> <li>Allows families to choose the measures of importance</li> <li>Easier communication with busy clinicians</li> <li>Feasible for children with advanced disease</li> </ul>
Mobile apps	<ul style="list-style-type: none"> <li>Can be used by parent, child or both allowing inter-relationship analysis across a variety of symptoms</li> <li>Direct reporting to clinicians</li> <li>Ability to provide targeted interventions focusing on non-pharmacologic therapies</li> </ul>	<ul style="list-style-type: none"> <li>Measures within apps vary, making it hard for clinicians to understand results or compare across apps</li> <li>Availability only on some operating systems (e.g., Apple (Apple Inc., Cupertino, CA, USA) vs Android (Google, Mountain View, CA, USA))</li> </ul>	<ul style="list-style-type: none"> <li>Teaches and enhances patient coping skills</li> <li>Ability to teach mindfulness, guided imagery, and breathing techniques</li> <li>Applicable for research on pain, fatigue, etc.</li> </ul>
Therapeutic toys	<ul style="list-style-type: none"> <li>Promote social, emotional development</li> <li>Can reduce pain, stress, fear</li> <li>Mixed-media capability with toy and mobile app</li> <li>Engaged children who can assist in design ideas</li> </ul>	<ul style="list-style-type: none"> <li>Can be expensive to acquire for hospitals or patients/parents</li> <li>Toys must meet many hospital safety and compliance regulations</li> <li>Few options available</li> </ul>	<ul style="list-style-type: none"> <li>Utilized as distraction for procedures</li> <li>Engages a patient’s senses of smell, touch</li> <li>Children can use toys to communicate emotions and feelings</li> </ul>
Interdisciplinary Pediatric Palliative Care team	<ul style="list-style-type: none"> <li>Ease of assessment in inpatient and outpatient settings</li> <li>Benefit of multiple member assessment (physician, nursing, social work, chaplain, child life)</li> <li>Data supporting improved patient/family outcomes</li> </ul>	<ul style="list-style-type: none"> <li>Less feasible when patients are home</li> <li>Increased personnel and time needed</li> <li>Not available at all pediatric centers</li> </ul>	<ul style="list-style-type: none"> <li>Provides human connection for families</li> <li>Have ability to combine with any other strategy</li> <li>Provides medical opinion and puts treatment plan in place</li> </ul>

EMR: electronic medical record, HRQOL: health-related quality of life.

### 8. Discussion

Recent innovations in addressing symptoms hold great promise in improving the care of children with serious illness. PROs, computer-based mobile apps, and toys are innovative solutions to the challenge of accurate pediatric symptom assessment and management. At the same time, they highlight areas in which future efforts are needed to advance care. One such area is that of symptom and HRQOL assessment methodology. Appreciation for the way in which a global view of a child’s experience is best obtained by self-report in conjunction with proxy-report is mounting. However, this must be accompanied by better understanding of what drives differences between these reporters, and how each perspective can best be understood in the context of the child’s total experience. As described in this paper, further instrument development is also imperative to improve psychometrics and standardization. With regard to the latter, this will require some consensus pertaining to the most important outcomes to capture. Within palliative care, PRO research that captures a child’s end-of-life experience is a particular need. Challenges to such work do exist; the child may be too sick to self-report during times of very advanced illness and highly emotionally charged circumstances. That being said, sensitivity, combined with a rigorous approach to this research, can overcome these challenges.

While still relatively early in development, systems for eliciting symptom and HRQOL data exist to facilitate efficient collection of longitudinal data and optimal medical care. Through technology-based collection of PRO, care is enhanced, including shared decision-making, effective communication and patient-centered care. At the same time we must guard against the possibility of moving from “high touch” to “high tech” care. Electronic medical records are gradually becoming more compatible with routine PRO assessment, allowing integration of reports. If PRO assessments are not tied to clinical encounters, systems and resources to address patient reports outside of clinical appointments in a timely manner will also be necessary.

We are just now scratching the surface of other PRO applications that extend beyond the point of care, such as evaluation of care quality, effectiveness, and value. These aspects of care have historically been measured in terms of care processes or downstream outcomes (e.g., readmission rates). In this age of value-based medicine, reimbursement is increasingly tied to patient outcomes as opposed to procedure or visit-based reimbursement. With value-based care placing greater emphasis on patient experience, such as patient well-being, now is the time for the incorporation of standardized measurement of PRO. PRO can thus become important indicators (performance measures) of provider and organizational performance, complementing other performance measures based in clinical outcomes and health care processes. Use of PRO in this regard further highlights the need to integrate PRO collection into electronic medical records.

Availing ourselves of the potential opportunities afforded by PRO assessment will necessitate overcoming barriers. First, optimal practices with regard to electronic administration of assessments (e.g., online versus app-based) must be delineated. The chosen methods must possess protections for patient privacy and confidentiality. Ideally these methods will also remain viable and compatible in the face of rapidly changing technology. Clinician buy-in to use these technologies can be achieved through involvement of clinicians in the development of PRO assessment practices as well as clinician education and staff training for maximum efficiency. A greater challenge may be organizational in nature. For example, a recent survey of pediatricians from 52 countries revealed largely organizational barriers to their assessment and use in clinical practice, including time, insufficient staff, logistical challenges, and financial resources [65].

Similar barriers will exist to more widespread use of computer-based or mobile apps. As patients, families, and clinicians have an increasing variety and number of choices to track and manage symptoms, it will become difficult to understand the measures, science, and methods behind each app. It would also become impractical for a physician to link with patients across multiple different sites. In starting to use a technology, collaboration with industry partners and information technology services may be needed to assist with installation and patient/clinician efficiency. Once mobile utilization has started, continual effort will be required to limit practice variation through quality improvement research and initiatives.

While all of the former methods are highly reliant upon technology incorporation into standard clinical practice, routinely integrating pediatric palliative care into the care of children will shift the culture of care to one emphasizing comfort and quality of life, regardless of treatment plan or outcome. Despite an increasing body of literature supporting pediatric palliative care integration as a standard of care for many children with complex, chronic, and life-threatening illness, utilization in practice has been slow. Several limitations remain to better integration including the size of the pediatric palliative care workforce, the comfort and knowledge of the pediatric clinicians, the system-level support, a billing infrastructure that values quality, and the ability to collaborate with local and state community organizations. When palliative care is better integrated, the lives of patients and families can be improved by focusing on symptom control, enhancing quality of life, and communicating well to enrich care coordination. Pediatric palliative care consultation combined with patient PRO may be an even more powerful approach to improving child HRQOL and should be investigated.

To the degree that disease-based screening, assessments, and treatments have improved over the years, the same attention needs to be paid to the patient experience. Novel approaches to improve the reporting of symptoms by patients and families, and the interpretation and management skills of clinicians are on the horizon. Yet, continued development and study of technological and team-based methods to improve symptom assessment and control are needed to drive palliative care forward.

**Author Contributions:** J.W. and C.U. conceived of the manuscript, K.E.B. and C.U. developed the manuscript outline, obtained references, and wrote the paper. The final manuscript was edited, reviewed, and agreed upon by all authors.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Feudtner, C.; Christakis, D.A.; Connell, F.A. Pediatric deaths attributable to complex chronic conditions: A population-based study of Washington State, 1980–1997. *Pediatrics* **2000**, *106*, 205–209. [PubMed]
2. Behrman, R.E.; Field, M.J. *When Children Die: Improving Palliative and End-of-Life Care for Children and Their Families—Summary*; The National Academies Press: Washington, DC, USA, 2003; p. 712.
3. Ries, L.A.G.; Smith, M.A.; Gurney, J.G.; Linet, M.; Tamra, T.; Young, J.L.; Bunin, G.R. *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995*; NIH Pub. No.99-4649; National Cancer Institute: Rockville, MD, USA, 1999.
4. Kestler, S.A.; LoBiondo-Wood, G. Review of symptom experiences in children and adolescents with cancer. *Cancer Nurs.* **2012**, *35*, E31–E49. [CrossRef] [PubMed]
5. Wolfe, J.; Orellana, L.; Ullrich, C.; Cook, E.F.; Kang, T.I.; Rosenberg, A.; Geyer, R.; Feudtner, C.; Dussel, V. Symptoms and distress in children with advanced cancer: Prospective Patient-reported outcomes from the PediQUEST Study. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2015**, *33*, 1928–1935. [CrossRef] [PubMed]
6. Ruland, C.M.; Hamilton, G.A.; Schjodt-Osmo, B. The complexity of symptoms and problems experienced in children with cancer: A review of the literature. *J. Pain Symptom Manag.* **2009**, *37*, 403–418. [CrossRef] [PubMed]
7. Fortier, M.A.; Sender, L.S.; Kain, Z.N. Management of pediatric oncology pain in the home setting: The next frontier. *J. Pediatr. Hematol. Oncol.* **2011**, *33*, 249–250. [CrossRef] [PubMed]
8. Lai, J.S.; Yount, S.; Beaumont, J.L.; Cella, D.; Toia, J.; Goldman, S. A patient-centered symptom monitoring and reporting system for children and young adults with cancer (SyMon-SAYS). *Pediatr. Blood Cancer* **2015**, *62*, 1813–1818. [CrossRef] [PubMed]
9. Cleeland, C.S. Cancer-related symptoms. *Semin. Radiat. Oncol.* **2000**, *10*, 175–190. [CrossRef] [PubMed]
10. Aronson, L. “Good” patients and “difficult” patients—rethinking our definitions. *N. Engl. J. Med.* **2013**, *369*, 796–797. [CrossRef] [PubMed]
11. Woodgate, R.L.; Degner, L.F. Expectations and beliefs about children’s cancer symptoms: Perspectives of children with cancer and their families. *Oncol. Nurs. Forum* **2003**, *30*, 479–491. [CrossRef] [PubMed]
12. Adams, D.; Schiffgen, M.; Kundu, A.; Dagenais, S.; Clifford, T.; Baydala, L.; King, W.J.; Vohra, S. Patterns of utilization of complementary and alternative medicine in 2 pediatric gastroenterology clinics. *J. Pediatr. Gastroenterol. Nutr.* **2014**, *59*, 334–339. [CrossRef] [PubMed]
13. Muriel, A.C.; Hwang, V.S.; Kornblith, A.; Greer, J.; Greenberg, D.B.; Temel, J.; Schapira, L.; Pirl, W. Management of psychosocial distress by oncologists. *Psychiatr. Serv.* **2009**, *60*, 1132–1134. [CrossRef] [PubMed]
14. Johnston, D.L.; Nagel, K.; Friedman, D.L.; Meza, J.L.; Hurwitz, C.A.; Friebert, S. Availability and use of palliative care and end-of-life services for pediatric oncology patients. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2008**, *26*, 4646–4650. [CrossRef] [PubMed]
15. Williams, P.D.; Williams, A.R.; Kelly, K.P.; Dobos, C.; Giesecking, A.; Connor, R.; Ridder, L.; Potter, N.; Del Favero, D. A symptom checklist for children with cancer: The Therapy-Related Symptom Checklist-Children. *Cancer Nurs.* **2012**, *35*, 89–98. [CrossRef] [PubMed]
16. Jibb, L.A.; Stevens, B.J.; Nathan, P.C.; Seto, E.; Cafazzo, J.A.; Johnston, D.L.; Hum, V.; Stinson, J.N. Implementation and preliminary effectiveness of a real-time pain management smartphone app for adolescents with cancer: A multicenter pilot clinical study. *Pediatr. Blood Cancer* **2017**, *64*, e26554. [CrossRef] [PubMed]
17. Fortier, M.A.; Chung, W.W.; Martinez, A.; Gago-Masague, S.; Sender, L. Pain buddy: A novel use of m-health in the management of children’s cancer pain. *Comput. Biol. Med.* **2016**, *76*, 202–214. [CrossRef] [PubMed]
18. Pinheiro, L.C.; McFatrigh, M.; Lucas, N.; Walker, J.S.; Withycombe, J.S.; Hinds, P.S.; Sung, L.; Tomlinson, D.; Freyer, D.R.; Mack, J.W.; et al. Child and adolescent self-report symptom measurement in pediatric oncology research: A systematic literature review. *Qual. Life Res.* **2017**, *27*, 291–319. [CrossRef] [PubMed]
19. Kaye, E.C.; Friebert, S.; Baker, J.N. Early Integration of palliative care for children with high-risk cancer and their families. *Pediatr. Blood Cancer* **2016**, *63*, 593–597. [CrossRef] [PubMed]
20. Pew Research Center, Washington, D.C. Mobile Fact Sheet. Available online: <http://www.pewinternet.org/fact-sheet/mobile/> (accessed on 15 November 2017).

21. Lenhart, A. Teens, Social Media & Technology Overview. 2015. Available online: <http://www.pewinternet.org/2015/04/09/teens-social-media-technology-2015/#fn-13190-1> (accessed on 21 January 2018).
22. Pew Research Center, Washington, D.C. Internet/Broadband Fact Sheet. Available online: <http://www.pewinternet.org/fact-sheet/internet-broadband/> (accessed on 15 November 2017).
23. Pew Research Center, Washington, D.C. Social Media Fact Sheet. Available online: <http://www.pewinternet.org/fact-sheet/social-media/> (accessed on 15 November 2017).
24. Gurol-Urganci, I.; de Jongh, T.; Vodopivec-Jamsek, V.; Atun, R.; Car, J. Mobile phone messaging reminders for attendance at healthcare appointments. *Cochrane Database Syst. Rev.* **2013**, *12*, CD007458. [[CrossRef](#)] [[PubMed](#)]
25. De Jongh, T.; Gurol-Urganci, I.; Vodopivec-Jamsek, V.; Car, J.; Atun, R. Mobile phone messaging for facilitating self-management of long-term illnesses. *Cochrane Database Syst. Rev.* **2012**, *12*, CD007459. [[CrossRef](#)] [[PubMed](#)]
26. Velikova, G.; Wright, E.P.; Smith, A.B.; Cull, A.; Gould, A.; Forman, D.; Perren, T.; Stead, M.; Brown, J.; Selby, P.J. Automated collection of quality-of-life data: A comparison of paper and computer touch-screen questionnaires. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **1999**, *17*, 998–1007. [[CrossRef](#)] [[PubMed](#)]
27. Wolpin, S.; Berry, D.; Austin-Seymour, M.; Bush, N.; Fann, J.R.; Halpenny, B.; Lober, W.B.; McCorkle, R. Acceptability of an Electronic Self-Report Assessment Program for patients with cancer. *Comput. Inform. Nurs.* **2008**, *26*, 332–338. [[CrossRef](#)] [[PubMed](#)]
28. Erharter, A.; Giesinger, J.; Kemmler, G.; Schauer-Maurer, G.; Stockhammer, G.; Muigg, A.; Hutterer, M.; Rumpold, G.; Sperner-Unterweger, B.; Holzner, B. Implementation of computer-based quality-of-life monitoring in brain tumor outpatients in routine clinical practice. *J. Pain Symptom Manag.* **2010**, *39*, 219–229. [[CrossRef](#)] [[PubMed](#)]
29. Abernethy, A.P.; Herndon, J.E., II; Wheeler, J.L.; Day, J.M.; Hood, L.; Patwardhan, M.; Shaw, M.; Lyerly, H.K. Feasibility and acceptability to patients of a longitudinal system for evaluating cancer-related symptoms and quality of life: Pilot study of an e/Tablet data-collection system in academic oncology. *J. Pain Symptom Manag.* **2009**, *37*, 1027–1038.
30. Belisario, J.S.M.; Jamsek, J.; Huckvale, K.; O'Donoghue, J.; Morrison, C.P.; Car, J. Comparison of self-administered survey questionnaire responses collected using mobile apps versus other methods. *Cochrane Database Syst. Rev.* **2015**, *7*, MR000042. [[CrossRef](#)] [[PubMed](#)]
31. Vinney, L.A.; Grade, J.D.; Connor, N.P. Feasibility of using a handheld electronic device for the collection of patient reported outcomes data from children. *J. Commun. Disord.* **2012**, *45*, 12–19. [[CrossRef](#)] [[PubMed](#)]
32. Velikova, G.; Keding, A.; Harley, C.; Cocks, K.; Booth, L.; Smith, A.B.; Wright, P.; Selby, P.J.; Brown, J.M. Patients report improvements in continuity of care when quality of life assessments are used routinely in oncology practice: Secondary outcomes of a randomised controlled trial. *Eur. J. Cancer* **2010**, *46*, 2381–2388. [[CrossRef](#)] [[PubMed](#)]
33. Detmar, S.B.; Muller, M.J.; Schornagel, J.H.; Wever, L.D.; Aaronson, N.K. Health-related quality-of-life assessments and patient-physician communication: A randomized controlled trial. *J. Am. Med. Assoc.* **2002**, *288*, 3027–3034. [[CrossRef](#)]
34. Carlson, L.E.; Specia, M.; Hagen, N.; Taenzer, P. Computerized quality-of-life screening in a cancer pain clinic. *J. Palliat. Care* **2001**, *17*, 46–52. [[PubMed](#)]
35. Velikova, G.; Booth, L.; Smith, A.B.; Brown, P.M.; Lynch, P.; Brown, J.M.; Selby, P.J. Measuring quality of life in routine oncology practice improves communication and patient well-being: A randomized controlled trial. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2004**, *22*, 714–724. [[CrossRef](#)] [[PubMed](#)]
36. Taenzer, P.; Bultz, B.D.; Carlson, L.E.; Specia, M.; DeGagne, T.; Olson, K.; Doll, R.; Rosberger, Z. Impact of computerized quality of life screening on physician behaviour and patient satisfaction in lung cancer outpatients. *Psycho-Oncology* **2000**, *9*, 203–213. [[CrossRef](#)]
37. Mark, T.L.; Fortner, B.; Johnson, G. Evaluation of a tablet PC technology to screen and educate oncology patients. *Support. Care Cancer Off. J. Multinat. Assoc. Support. Care Cancer* **2008**, *16*, 371–378. [[CrossRef](#)] [[PubMed](#)]
38. Ruland, C.M.; White, T.; Stevens, M.; Fanciullo, G.; Khilani, S.M. Effects of a computerized system to support shared decision making in symptom management of cancer patients: Preliminary results. *J. Am. Med. Assoc.* **2003**, *10*, 573–579. [[CrossRef](#)] [[PubMed](#)]

39. Hockenberry, M.J.; Hinds, P.S.; Barrera, P.; Bryant, R.; Adams-McNeill, J.; Hooke, C.; Rasco-Baggott, C.; Patterson-Kelly, K.; Gattuso, J.S.; Manteuffel, B. Three instruments to assess fatigue in children with cancer: The child, parent and staff perspectives. *J. Pain Symptom Manag.* **2003**, *25*, 319–328. [[CrossRef](#)]
40. Glaser, A.W.; Davies, K.; Walker, D.; Brazier, D. Influence of proxy respondents and mode of administration on health status assessment following central nervous system tumours in childhood. *Qual. Life Res.* **1997**, *6*, 43–53. [[CrossRef](#)] [[PubMed](#)]
41. Drakouli, M.; Petsios, K.; Giannakopoulou, M.; Patiraki, E.; Voutoufianaki, I.; Matziou, V. Determinants of quality of life in children and adolescents with CHD: A systematic review. *Cardiol. Young* **2015**, *25*, 1027–1036. [[CrossRef](#)] [[PubMed](#)]
42. Amedro, P.; Dorka, R.; Moniotte, S.; Guillaumont, S.; Fraisse, A.; Kreitmann, B.; Borm, B.; Bertet, H.; Barrea, C.; Ovaert, C.; et al. Quality of Life of Children with Congenital Heart Diseases: A Multicenter Controlled Cross-Sectional Study. *Pediatr. Cardiol.* **2015**, *36*, 1588–1601. [[CrossRef](#)] [[PubMed](#)]
43. Ullrich, C.K.; Rodday, A.M.; Bingen, K.M.; Kupst, M.J.; Patel, S.K.; Syrjala, K.L.; Harris, L.L.; Recklitis, C.J.; Chang, G.; Guinan, E.C.; et al. Three sides to a story: Child, parent, and nurse perspectives on the child's experience during hematopoietic stem cell transplantation. *Cancer* **2017**, *123*, 3159–3166. [[CrossRef](#)] [[PubMed](#)]
44. Panepinto, J.A.; O'Mahar, K.M.; DeBaun, M.R.; Loberiza, F.R.; Scott, J.P. Health-related quality of life in children with sickle cell disease: Child and parent perception. *Br. J. Haematol.* **2005**, *130*, 437–444. [[CrossRef](#)] [[PubMed](#)]
45. Rajmil, L.; Lopez, A.R.; Lopez-Aguila, S.; Alonso, J. Parent-child agreement on health-related quality of life (HRQOL): A longitudinal study. *Health Qual. Life Outcomes* **2013**, *11*, 101. [[CrossRef](#)] [[PubMed](#)]
46. Eiser, C.; Morse, R. Can parents rate their child's health-related quality of life? Results of a systematic review. *Qual. Life Res.* **2001**, *10*, 347–357. [[CrossRef](#)] [[PubMed](#)]
47. Weaver, M.S.; Darnall, C.; Bace, S.; Vail, C.; MacFadyen, A.; Wichman, C. Trending Longitudinal Agreement between Parent and Child Perceptions of Quality of Life for Pediatric Palliative Care Patients. *Children* **2017**, *4*, 65. [[CrossRef](#)] [[PubMed](#)]
48. Rapp, M.; Eisemann, N.; Arnaud, C.; Ehlinger, V.; Fauconnier, J.; Marcelli, M.; Michelsen, S.I.; Nystrand, M.; Colver, A.; Thyen, U. Predictors of parent-reported quality of life of adolescents with cerebral palsy: A longitudinal study. *Res. Dev. Disabil.* **2017**, *62*, 259–270. [[CrossRef](#)] [[PubMed](#)]
49. Aspesberro, F.; Mangione-Smith, R.; Zimmerman, J.J. Health-related quality of life following pediatric critical illness. *Intensive Care Med.* **2015**, *41*, 1235–1246. [[CrossRef](#)] [[PubMed](#)]
50. Rodday, A.M.; Terrin, N.; Leslie, L.K.; Graham, R.J.; Parsons, S.K. Understanding the Relationship Between Child Health-Related Quality of Life and Parent Emotional Functioning in Pediatric Hematopoietic Stem Cell Transplant. *J. Pediatr. Psychol.* **2017**, *42*, 804–814. [[CrossRef](#)] [[PubMed](#)]
51. U.S. Food and Drug Administration. Guidance for Industry: Patient-reported outcome measures—Use in medical product development to support labeling claims. *Fed. Regist.* **2009**, *74*, 65132–65133.
52. Meldahl, M.L.; Acaster, S.; Hayes, R.P. Exploration of oncologists' attitudes toward and perceived value of patient-reported outcomes. *Qual. Life Res.* **2013**, *22*, 725–731. [[CrossRef](#)] [[PubMed](#)]
53. Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Available online: <https://healthcaresdelivery.cancer.gov/pro-ctcae/> (accessed on 21 November 2017).
54. Basch, E.; Dueck, A.C.; Rogak, L.J.; Minasian, L.M.; Kelly, W.K.; O'Mara, A.M.; Denicoff, A.M.; Seisler, D.; Atherton, P.J.; Paskett, E.; et al. Feasibility Assessment of patient reporting of symptomatic adverse events in multicenter cancer clinical trials. *JAMA Oncol.* **2017**, *3*, 1043–1050. [[CrossRef](#)] [[PubMed](#)]
55. Basch, E.; Deal, A.M.; Kris, M.G.; Scher, H.I.; Hudis, C.A.; Sabbatini, P.; Rogak, L.; Bennett, A.V.; Dueck, A.C.; Atkinson, T.M.; et al. Symptom Monitoring with patient-reported outcomes during routine cancer treatment: A randomized controlled trial. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2016**, *34*, 557–565. [[CrossRef](#)] [[PubMed](#)]
56. Basch, E.; Deal, A.M.; Dueck, A.C.; Scher, H.I.; Kris, M.G.; Hudis, C.; Schrag, D. Overall Survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *J. Am. Med. Assoc.* **2017**, *318*, 197–198. [[CrossRef](#)] [[PubMed](#)]
57. Rotenstein, L.S.; Huckman, R.S.; Wagle, N.W. Making Patients and doctors happier—The Potential of patient-reported outcomes. *N. Engl. J. Med.* **2017**, *377*, 1309–1312. [[CrossRef](#)] [[PubMed](#)]

58. Brundage, M.; Blackford, A.; Tolbert, E.; Smith, K.; Bantug, E.; Snyder, C.; Board, P.D. Presenting comparative study PRO results to clinicians and researchers: Beyond the eye of the beholder. *Qual. Life Res.* **2018**, *27*, 75–90. [[CrossRef](#)] [[PubMed](#)]
59. Bantug, E.T.; Coles, T.; Smith, K.C.; Snyder, C.F.; Rouette, J.; Brundage, M.D.; Board, P.D. Graphical displays of patient-reported outcomes (PRO) for use in clinical practice: What makes a pro picture worth a thousand words? *Patient Educ. Couns.* **2016**, *99*, 483–490. [[CrossRef](#)] [[PubMed](#)]
60. Dobrozsi, S.; Panepinto, J. Child and parent preferences for graphical display of patient-reported outcome data. *Pediatr. Blood Cancer* **2017**, *64*. [[CrossRef](#)] [[PubMed](#)]
61. U.S. National Library of Medicine. Available online: <https://clinicaltrials.gov/> (accessed on 26 March 2018).
62. Fayed, N.; de Camargo, O.K.; Elahi, I.; Dubey, A.; Fernandes, R.M.; Houtrow, A.; Cohen, E. Patient-important activity and participation outcomes in clinical trials involving children with chronic conditions. *Qual. Life Res.* **2014**, *23*, 751–757. [[CrossRef](#)] [[PubMed](#)]
63. Reeve, B.B.; Edwards, L.J.; Jaeger, B.C.; Hinds, P.S.; Dampier, C.; Gipson, D.S.; Selewski, D.T.; Troost, J.P.; Thissen, D.; Barry, V.; et al. Assessing responsiveness over time of the PROMIS pediatric symptom and function measures in cancer, nephrotic syndrome, and sickle cell disease. *Qual. Life Res.* **2017**, *27*, 249–257. [[CrossRef](#)] [[PubMed](#)]
64. Reeve, B.B.; McFatrach, M.; Pinheiro, L.C.; Weaver, M.S.; Sung, L.; Withycombe, J.S.; Baker, J.N.; Mack, J.W.; Waldron, M.K.; Gibson, D.; et al. Eliciting the child’s voice in adverse event reporting in oncology trials: Cognitive interview findings from the Pediatric Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events initiative. *Pediatr. Blood Cancer* **2017**, *64*, e26261. [[CrossRef](#)] [[PubMed](#)]
65. Schepers, S.A.; Haverman, L.; Zadeh, S.; Grootenhuis, M.A.; Wiener, L. Healthcare Professionals’ Preferences and Perceived Barriers for Routine Assessment of Patient-Reported Outcomes in Pediatric Oncology Practice: Moving Toward International Processes of Change. *Pediatr. Blood Cancer* **2016**, *63*, 2181–2188. [[CrossRef](#)] [[PubMed](#)]
66. Huang, I.C.; Revicki, D.A.; Schwartz, C.E. Measuring pediatric patient-reported outcomes: Good progress but a long way to go. *Qual. Life Res.* **2014**, *23*, 747–750. [[CrossRef](#)] [[PubMed](#)]
67. Anthony, S.J.; Selkirk, E.; Sung, L.; Klaassen, R.J.; Dix, D.; Scheinemann, K.; Klassen, A.F. Considering quality of life for children with cancer: A systematic review of patient-reported outcome measures and the development of a conceptual model. *Qual. Life Res.* **2014**, *23*, 771–789. [[CrossRef](#)] [[PubMed](#)]
68. Janssens, A.; Thompson Coon, J.; Rogers, M.; Allen, K.; Green, C.; Jenkinson, C.; Tennant, A.; Logan, S.; Morris, C. A systematic review of generic multidimensional patient-reported outcome measures for children, part I: Descriptive characteristics. *Value Health* **2015**, *18*, 315–333. [[CrossRef](#)] [[PubMed](#)]
69. PROMIS. Available online: <http://www.healthmeasures.net/explore-measurement-systems/promis> (accessed on 29 November 2017).
70. DeWitt, E.M.; Stucky, B.D.; Thissen, D.; Irwin, D.E.; Langer, M.; Varni, J.W.; Lai, J.S.; Yeatts, K.B.; Dewalt, D.A. Construction of the eight-item patient-reported outcomes measurement information system pediatric physical function scales: Built using item response theory. *J. Clin. Epidemiol.* **2011**, *64*, 794–804. [[CrossRef](#)] [[PubMed](#)]
71. Irwin, D.E.; Stucky, B.D.; Thissen, D.; Dewitt, E.M.; Lai, J.S.; Yeatts, K.; Varni, J.W.; DeWalt, D.A. Sampling plan and patient characteristics of the PROMIS pediatrics large-scale survey. *Qual. Life Res.* **2010**, *19*, 585–594. [[CrossRef](#)] [[PubMed](#)]
72. Varni, J.W.; Stucky, B.D.; Thissen, D.; Dewitt, E.M.; Irwin, D.E.; Lai, J.S.; Yeatts, K.; Dewalt, D.A. PROMIS Pediatric Pain Interference Scale: An item response theory analysis of the pediatric pain item bank. *J. Pain* **2010**, *11*, 1109–1119. [[CrossRef](#)] [[PubMed](#)]
73. Quinn, H.; Thissen, D.; Liu, Y.; Magnus, B.; Lai, J.S.; Amtmann, D.; Varni, J.W.; Gross, H.E.; DeWalt, D.A. Using item response theory to enrich and expand the PROMIS(R) pediatric self report banks. *Health Qual. Life Outcomes* **2014**, *12*, 160. [[CrossRef](#)] [[PubMed](#)]
74. Irwin, D.E.; Gross, H.E.; Stucky, B.D.; Thissen, D.; DeWitt, E.M.; Lai, J.S.; Amtmann, D.; Khastou, L.; Varni, J.W.; DeWalt, D.A. Development of six PROMIS pediatrics proxy-report item banks. *Health Qual. Life Outcomes* **2012**, *10*, 22. [[CrossRef](#)] [[PubMed](#)]

75. Reeve, B.B.; Thissen, D.; DeWalt, D.A.; Huang, I.C.; Liu, Y.; Magnus, B.; Quinn, H.; Gross, H.E.; Kisala, P.A.; Ni, P.; et al. Linkage between the PROMIS(R) pediatric and adult emotional distress measures. *Qual. Life Res.* **2016**, *25*, 823–833. [[CrossRef](#)] [[PubMed](#)]
76. Barthel, D.; Fischer, K.I.; Nolte, S.; Otto, C.; Meyrose, A.K.; Reisinger, S.; Dabs, M.; Thyen, U.; Klein, M.; Muehlan, H.; et al. Implementation of the Kids-CAT in clinical settings: A newly developed computer-adaptive test to facilitate the assessment of patient-reported outcomes of children and adolescents in clinical practice in Germany. *Qual. Life Res.* **2016**, *25*, 585–594. [[CrossRef](#)] [[PubMed](#)]
77. Devine, J.; Otto, C.; Rose, M.; Barthel, D.; Fischer, F.; Muhlan, H.; Nolte, S.; Schmidt, S.; Ottova-Jordan, V.; Ravens-Sieberer, U. A new computerized adaptive test advancing the measurement of health-related quality of life (HRQoL) in children: The Kids-CAT. *Qual. Life Res.* **2015**, *24*, 871–884. [[CrossRef](#)] [[PubMed](#)]
78. Barthel, D.; Otto, C.; Nolte, S.; Meyrose, A.K.; Fischer, F.; Devine, J.; Walter, O.; Mierke, A.; Fischer, K.I.; Thyen, U.; et al. The validation of a computer-adaptive test (CAT) for assessing health-related quality of life in children and adolescents in a clinical sample: Study design, methods and first results of the Kids-CAT study. *Qual. Life Res.* **2017**, *26*, 1105–1117. [[CrossRef](#)] [[PubMed](#)]
79. Wolfe, J.; Orellana, L.; Cook, E.F.; Ullrich, C.; Kang, T.; Geyer, J.R.; Feudtner, C.; Weeks, J.C.; Dussel, V. Improving the care of children with advanced cancer by using an electronic patient-reported feedback intervention: Results from the PediQUEST randomized controlled trial. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2014**, *32*, 1119–1126. [[CrossRef](#)] [[PubMed](#)]
80. Dussel, V.; Orellana, L.; Soto, N.; Chen, K.; Ullrich, C.; Kang, T.I.; Geyer, J.R.; Feudtner, C.; Wolfe, J. Feasibility of Conducting a Palliative Care Randomized Controlled Trial in Children With Advanced Cancer: Assessment of the PediQUEST Study. *J. Pain Symptom Manag.* **2015**, *49*, 1059–1069. [[CrossRef](#)] [[PubMed](#)]
81. Haverman, L.; van Oers, H.; Limperg, P.F.L.; Hijmans, C.T.; Schepers, S.A.; Sint Nicolas, S.M.; Verhaak, C.M.; Bouts, A.H.M.; Fijnvandraat, K.; Peters, M.; et al. Implementation of Electronic Patient Reported Outcomes in Pediatric Daily Clinical Practice: The KLIK Experience. *Clin. Pract. Pediatr. Psychol.* **2014**, *2*, 50–67. [[CrossRef](#)]
82. Haverman, L.; van Rossum, M.A.; van Veenendaal, M.; van den Berg, J.M.; Dolman, K.M.; Swart, J.; Kuijpers, T.W.; Grootenhuis, M.A. Effectiveness of a web-based application to monitor health-related quality of life. *Pediatrics* **2013**, *131*, e533–e543. [[CrossRef](#)] [[PubMed](#)]
83. Haverman, L.; Engelen, V.; van Rossum, M.A.; Heymans, H.S.; Grootenhuis, M.A. Monitoring health-related quality of life in paediatric practice: Development of an innovative web-based application. *BMC Pediatr.* **2011**, *11*, 3. [[CrossRef](#)] [[PubMed](#)]
84. Engelen, V.; van Zwieten, M.; Koopman, H.; Detmar, S.; Caron, H.; Brons, P.; Egeler, M.; Kaspers, G.J.; Grootenhuis, M. The influence of patient reported outcomes on the discussion of psychosocial issues in children with cancer. *Pediatr. Blood Cancer* **2012**, *59*, 161–166. [[CrossRef](#)] [[PubMed](#)]
85. Engelen, V.; Detmar, S.; Koopman, H.; Maurice-Stam, H.; Caron, H.; Hoogerbrugge, P.; Egeler, R.M.; Kaspers, G.; Grootenhuis, M. Reporting health-related quality of life scores to physicians during routine follow-up visits of pediatric oncology patients: Is it effective? *Pediatr. Blood Cancer* **2012**, *58*, 766–774. [[CrossRef](#)] [[PubMed](#)]
86. My Quality Ltd. My Quality. Available online: <https://my-quality.Net/> (accessed on 26 March 2018).
87. Harris, N.; Beringer, A.; Fletcher, M. Families' priorities in life-limiting illness: Improving quality with online empowerment. *Arch. Dis. Child.* **2016**, *101*, 247–252. [[CrossRef](#)] [[PubMed](#)]
88. Symple health, Inc. Symple. <https://www.Sympleapp.com/> (accessed on 26 March 2018).
89. Connelly, M.; Bromberg, M.H.; Anthony, K.K.; Gil, K.M.; Schanberg, L.E. Use of smartphones to prospectively evaluate predictors and outcomes of caregiver responses to pain in youth with chronic disease. *Pain* **2016**, *158*, 629–636. [[CrossRef](#)] [[PubMed](#)]
90. Smith, K.; Iversen, C.; Kossowsky, J.; O'Dell, S.; Gambhir, R.; Coakley, R. Apple apps for the management of pediatric pain and pain-related stress. *Clin. Pract. Pediatr. Psychol.* **2015**, *3*, 93–107. [[CrossRef](#)]
91. Children's Hospitals and Clinics of Minnesota, Ridgeview Medical Center, and DesignWise Medical. Healing Buddies Comfort Kit. Available online: <http://www.Healingbuddiescomfort.org/> (accessed on 26 March 2018).
92. Holgersen, P. Mindful-app. Available online: [www.mindful-app.com](http://www.mindful-app.com) (accessed on 26 March 2018).
93. Price, S. Positive Penguins. Available online: [www.positivepenguins.com](http://www.positivepenguins.com) (accessed on 26 March 2018).
94. Kiche, M.T.; de Amorim Almeida, F. Therapeutic toy: Strategy for pain management and tension relief during dressing change in children. *Acta Paul. Enferm.* **2009**, *22*, 125–130. [[CrossRef](#)]
95. Sproutel, Inc. Jerry the Bear. Available online: [www.jerrythebear.com](http://www.jerrythebear.com) (accessed on 26 March 2018).

96. Schmidt, P.; Otto, M.; Hechler, T.; Metzger, S.; Wolfe, J.; Zernikow, B. Did increased availability of pediatric palliative care lead to improved palliative care outcomes in children with cancer? *J. Palliat. Med.* **2013**, *16*, 1034–1039. [[CrossRef](#)] [[PubMed](#)]
97. Snaman, J.M.; Kaye, E.C.; Lu, J.J.; Sykes, A.; Baker, J.N. Palliative Care Involvement Is Associated with Less Intensive End-of-Life Care in Adolescent and Young Adult Oncology Patients. *J. Palliat. Med.* **2017**, *20*, 509–516. [[CrossRef](#)] [[PubMed](#)]
98. Levine, D.R.; Johnson, L.M.; Snyder, A.; Wisner, R.K.; Gibson, D.; Kane, J.R.; Baker, J.N. Integrating Palliative Care in Pediatric Oncology: Evidence for an Evolving Paradigm for Comprehensive Cancer Care. *J. Natl. Compr. Cancer Netw.* **2016**, *14*, 741–748. [[CrossRef](#)]
99. Levine, D.R.; Mandrell, B.N.; Sykes, A.; Pritchard, M.; Gibson, D.; Symons, H.J.; Wendler, D.; Baker, J.N. Patients' and Parents' Needs, Attitudes, and Perceptions About Early Palliative Care Integration in Pediatric Oncology. *JAMA Oncol.* **2017**, *3*, 1214–1220. [[CrossRef](#)] [[PubMed](#)]
100. Waldman, E.; Wolfe, J. Palliative care for children with cancer. *Nat. Rev. Clin. Oncol.* **2013**, *10*, 100–107. [[CrossRef](#)] [[PubMed](#)]
101. Weaver, M.S.; Heinze, K.E.; Bell, C.J.; Wiener, L.; Garee, A.M.; Kelly, K.P.; Casey, R.L.; Watson, A.; Hinds, P.S. Establishing psychosocial palliative care standards for children and adolescents with cancer and their families: An integrative review. *Palliat. Med.* **2016**, *30*, 212–223. [[CrossRef](#)] [[PubMed](#)]
102. Wolfe, J.; Friebert, S.; Hilden, J. Caring for children with advanced cancer integrating palliative care. *Pediatr. Clin. N. Am.* **2002**, *49*, 1043–1062. [[CrossRef](#)]
103. Kaye, E.C.; Rubenstein, J.; Levine, D.; Baker, J.N.; Dabbs, D.; Friebert, S.E. Pediatric palliative care in the community. *Cancer J. Clin.* **2015**, *65*, 316–333. [[CrossRef](#)] [[PubMed](#)]
104. Yennurajalingam, S.; Urbauer, D.L.; Casper, K.L.; Reyes-Gibby, C.C.; Chacko, R.; Poulter, V.; Bruera, E. Impact of a palliative care consultation team on cancer-related symptoms in advanced cancer patients referred to an outpatient supportive care clinic. *J. Pain Symptom Manag.* **2011**, *41*, 49–56. [[CrossRef](#)] [[PubMed](#)]
105. Muir, J.C.; Daly, F.; Davis, M.S.; Weinberg, R.; Heintz, J.S.; Paivanas, T.A.; Beveridge, R. Integrating palliative care into the outpatient, private practice oncology setting. *J. Pain Symptom Manag.* **2010**, *40*, 126–135. [[CrossRef](#)] [[PubMed](#)]
106. Kaye, E.C.; Snaman, J.M.; Baker, J.N. Pediatric Palliative oncology: Bridging Silos of care through an embedded model. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2017**, *35*, 2740–2744. [[CrossRef](#)] [[PubMed](#)]
107. Wu, W.W.; Johnson, R.; Schepp, K.G.; Berry, D.L. Electronic self-report symptom and quality of life for adolescent patients with cancer: A feasibility study. *Cancer Nurs.* **2011**, *34*, 479–486. [[CrossRef](#)] [[PubMed](#)]
108. Cagle, J.G.; Osteen, P.; Sacco, P.; Jacobson Frey, J. Psychosocial Assessment by Hospice Social Workers: A Content Review of Instruments From a National Sample. *J. Pain Symptom Manag.* **2017**, *53*, 40–48. [[CrossRef](#)] [[PubMed](#)]
109. McSherry, M.; Kehoe, K.; Carroll, J.M.; Kang, T.I.; Rourke, M.T. Psychosocial and spiritual needs of children living with a life-limiting illness. *Pediatr. Clin. N. Am.* **2007**, *54*, 609–629. [[CrossRef](#)] [[PubMed](#)]
110. Edlynn, E.; Kaur, H. The role of psychology in pediatric palliative care. *J. Palliat. Med.* **2016**, *19*, 760–762. [[CrossRef](#)] [[PubMed](#)]
111. DiScala, S.L.; Onofrio, S.; Miller, M.; Nazario, M.; Silverman, M. Integration of a clinical pharmacist into an interdisciplinary palliative care outpatient clinic. *Am. J. Hosp. Palliat. Care* **2017**, *34*, 814–819. [[CrossRef](#)] [[PubMed](#)]
112. Estacio, C.F.; Butow, P.N.; Lovell, M.R.; Dong, S.T.; Clayton, J.M. What is symptom meaning? A framework analysis of communication in palliative care consultations. *Patient Educ. Couns.* **2017**, *100*, 2088–2094. [[CrossRef](#)] [[PubMed](#)]

