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Commentary

Patient-Reported Outcomes in Pediatric Cancer Registration Trials: A US Food and Drug Administration Perspective

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COMMENTARY

Abstract

Pediatric patient-reported outcome (PRO) data can help inform the US Food and Drug Administration's (FDA's) benefit-risk assessment of cancer therapeutics by quantifying symptom and functional outcomes from the patient's perspective. This study assessed use of PROs in commercial pediatric oncology trials submitted to the FDA for regulatory review. FDA databases were searched to identify pediatric oncology product applications approved between 1997 and 2020. Sponsor-submitted documents were reviewed to determine whether PRO data were collected, which instruments were used, and the quality of collected data (ie, sample size, completion rates, and use of fit-for-purpose instruments). The role of PROs in each trial (endpoint hierarchy) was also recorded in addition to whether any PRO endpoints were included in product labeling. We reviewed 17 pediatric oncology applications, 4 of which included PRO data: denosumab, tisagenlecleucel, larotrectinib, and selumetinib. In these 4 instances, PROs served as exploratory endpoints and were not incorporated in product labeling. Trials that collected PRO data were phase II or phase I/II single-arm studies with sample sizes of 28 to 88 patients. Symptomatic adverse events (AEs) were characterized using clinician-reported Common Terminology Criteria for Adverse Events (CTCAE) without additional patient self-report. PROs were infrequently used in pediatric cancer registration trials. When PROs were used, PRO data were limited by lack of a clear research objective and corresponding prospective statistical analysis plan. Contemporary PRO symptom libraries, such as the National Cancer Institute's Pediatric PRO-CTCAE, may provide an opportunity to better evaluate the occurrence and impact of symptomatic AEs, from the patient's perspective, in pediatric oncology trials.

The 21st Century Cures Act directed the US Food and Drug Administration (FDA) to systematically incorporate patients' experiences, needs, perspectives, and priorities into drug development and evaluation (1). Patients are experts in their disease because of their lived experience with its symptoms and treatment, and this includes children. In completing patient-reported outcome (PRO) measures that are fit for purpose, patients of different ages can provide unique and valuable symptom and functional information to help inform the FDA's benefit-risk assessment of cancer therapeutics.

The collection of PRO data in adult cancer clinical trials has allowed for enhanced and more accurate reporting of symptomatic adverse events (AEs) (2,3). Emerging evidence also suggests that using PRO assessments to monitor symptoms during routine cancer care can lead to an improvement in clinical outcomes, including survival (4,5). Despite these benefits observed in adult patients with cancer, there has been a dearth of work specific to PROs in pediatric oncology drug development. Studies have demonstrated that clinicians and caregivers frequently under- or overestimate the prevalence, intensity, and burden of symptomatic AEs compared with children's self-report (6-10). Therefore, pediatric PRO data can provide a more comprehensive assessment of the safety and tolerability profile of cancer therapeutics. Similar to efforts in adult patients, these data can be used in clinical practice to improve communication and shared decision making between clinicians and patients/caregivers about side effect recognition, management, and supportive care, with the goal of maximizing the child's quality of life (QOL). Thus, patient experience data can help regulators and ultimately prescribers, caregivers, patients, and payers make more informed decisions regarding use of anticancer drugs in pediatric populations (11).

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The FDA's Oncology Center of Excellence (OCE) is committed to thoughtful incorporation of clinical outcome assessments into drug development. The overarching aim of this article is to describe the current status of PROs in pediatric cancer registration trials and provide the FDA's perspectives for future directions to ensure that the Patient-Focused Drug Development (PFDD) initiative benefits patients of all ages.

Methods

Sample Identification

We used internal FDA databases to identify pediatric oncology product applications and their associated trials submitted for regulatory review. We included all original or supplemental new drug applications and biologics license applications approved by the Office of Oncologic Diseases (formerly the Office for Hematology and Oncology Products). Products were excluded if they were approved for pediatric indications solely based on extrapolation of efficacy from data in adults and pediatric pharmacokinetic data. We restricted our analysis to applications approved between passing of the Food and Drug Administration Modernization Act in 1997, which spurred drug development in pediatric oncology, and April 2020, when the present study began.

Information Extraction From the Analytic Sample

We reviewed sponsor-submitted materials, including clinical study reports, protocols, and other summary documents. For each approved product, we abstracted general information regarding year of product approval, trial phase, study design, and sample size. In addition, we noted whether PRO data were collected in each trial and which instruments were used. We also recorded the role of PROs in each trial (primary, secondary, tertiary, or exploratory endpoint), along with whether any of these endpoints were included in the product label. When PRO data were available, we evaluated their quality based on sample size, attrition, reporting of completion rates, use of anchor-based methods to determine clinically significant changes, and submission of evidence supporting the validity and relevancy of each PRO instrument used. Completion rate was defined as the proportion of on-study subjects who were expected to receive a PRO assessment and filled in at least 1 question (12). This expected population excludes patients who died, had progressive disease, or otherwise withdrew from the trial. Patients with progressive disease were excluded because they generally discontinue treatment upon disease progression. For purposes of this study, completion rates were considered "not reported" if completion tables or figures were not provided in the clinical study report or other trial submission materials.

Results

Our review included 17 oncology products that were FDA approved for use in pediatric patients. Of these 17 product applications, only 4 collected and reported PRO data, and 1 additionally included a performance outcome measure (Table 1). All products with clinical outcome assessments were approved after publication of FDA's PRO guidance document in 2009 (13). Denosumab was approved for use in pediatric patients in 2013, tisagenlecleucel in 2017, larotrectinib in 2018, and selumetinib in 2020. PROs were treated as exploratory endpoints in each of these trials, and none of the PRO results were included in FDA product labeling.

In general, symptomatic AEs were characterized using clinician-reported Common Terminology Criteria for Adverse Events (CTCAE) and were not complemented with patients' self-report. Clinician-reported AEs were also not limited to objective or observable symptoms and side effects. The Pediatric Quality of Life Inventory (PedsQL) Generic Core Scale (Standard Version, with a 30-day recall period) was the most commonly used pediatric PRO instrument (3 of 4 trials). In trials using the PedsQL, a combination of pediatric self-report and the parent/guardian proxy report instruments were employed. Pediatric self-report was limited to use in patients aged 8 through 17 years, while parent proxy report was generally reserved for younger patients. All other PRO measures were symptom specific and often intended to measure patient-reported pain (eg, Brief Pain Inventory–Short Form) (14), the Wong-Baker Faces scale (15), an 11-point pain numeric rating scale, and the Pain Interference Index (16). The trial that used the 11-point numeric rating scale used this measure solely in patients aged 8 to 18 years for self-report. Meanwhile, the Pain Interference Index was completed through proxy report by parents/guardians for study participants between the ages of 5 and 18 years and through self-report for patients between the ages of 8 and 18 years.

When PRO data were collected, we observed that they were often limited to use in phase I/II or phase II single-arm trials with small sample sizes, ranging from 28 to 88 patients per trial. We also noted that PRO assessment completion rates were seldom reported. Of the 4 trials that incorporated PROs, only 1 reported PRO assessment completion rates. This single study reported baseline completion rates ranging from 25% (Dysfunction Voiding Questionnaire) to 97% (PedsQL Generic Core Scale) (Supplementary Table 1, available online). Also important to note is the proportion of the intention-to-treat population that remained on treatment in randomized trials and attrition in the case of single-arm trials. As would be expected in cancer clinical trials where patients discontinue treatment upon progression, we observed decreasing numbers of on-treatment study participants and a consequential decline in the number of PRO assessments completed over the course of each study. Finally, none of the trials we reviewed used anchor-based methods to determine whether a clinically meaningful within-patient score change in PROs was observed.

Discussion

Our review of 17 pediatric oncology trials submitted to the FDA revealed that clinical outcome assessments, and specifically PROs, were rarely collected and applied to pediatric oncology drug development. This finding may represent a lost opportunity because recent studies suggest that it is feasible to elicit patient-reported symptom data directly from patients as young as 7 years of age (10,17). Although our review spanned from 1997 to 2020, we noted that PROs were used in recent years only (from 2013 onward). Denosumab, tisagenlecleucel, larotrectinib, and selumetinib were the 4 product applications in our review that reported PRO data. In all 4 of these trials, PROs were treated as exploratory endpoints and not subsequently included in product labeling.

The decision to include information in the FDA label is multifactorial, with a focus on providing information that is accurate and not misleading. Sponsors that want to include PRO data in their labeling claims are encouraged to have early

Table 1. Patient-reported outcomes in US Food and Drug Administration–approved pediatric oncology product applications[a]

Medication	Indication	Pediatric approval, y	Phase and trial design	Sample size, No.	Study participants' age, median (range), y	PRO data reported?	PRO/COA measures	PRO endpoints included in labeling?
Clofarabine	ALL, refractory or relapsed AML	2004	Phase II, open label, single arm	42	13 (2-22)	No	NA	NA
Nelarabine	T-ALL or T-LBL	2005	Phase III, open label, randomized, multicenter	825	T-ALL: 10 (1-29), T-LBL: 10.5 (1-25)	No	NA	NA
Asparaginase (*Erwinia chrysanthemi*)	ALL	2011	Compassionate use, open label, single arm	927	9 (1-66)	No	NA	NA
Everolimus	SEGA with TCS	2012	Phase III, randomized, double blind, placebo controlled	117	9.5 (1.1-27.4)	No	NA	NA
Denosumab	Giant cell tumor of the bone	2013	Phase II, open label, single arm, multicenter	532, of which 28 were pediatric participants (adolescents aged 12-18 y)	16 (13-17) for the adolescent subgroup	Yes	BPI-SF (based on adolescent self-report)	Not included
Blinatumomab	Refractory or relapsed B-ALL	2014	Phase II, open label, single arm, multicenter	93	8 (birth to 17)	No	NA	NA
Dinutuximab	High-risk neuroblastoma	2015	Phase III, randomized, open label	251	3.8 (0.9-15.3)	No	NA	NA
Gemtuzumab	Relapsed/refractory CD33+ AML	2017	Phase III, randomized, open label	1063, of whom 29 were pediatric participants	8.7 (0.2-18)	No	NA	NA
Dasatinib	Ph+ CML	2017	Phase II, open label, single arm, multicenter	145	12 (1-20)	No	NA	NA
Imatinib	Ph+ ALL	2017	Phase II/III, randomized, open label, multicenter	126	9.4 (1.6-17.9)	No	NA	NA
Ipilimumab	Unresectable or metastatic melanoma	2017	Phase II, open label, single arm, multicenter	12	15 (12-16)	No	NA	NA
Tisagenlecleucel	Refractory or relapsed B-ALL	2017	Phase II, open label, single arm, multicenter	88	12.1 (3-27)	Yes	PedsQL 4.0 Generic Core, EQ-5D-Y	Not included
Pembrolizumab	Refractory cHL, MSI-H, or mismatch repair–deficient solid tumor, refractory primary mediastinal large B-cell lymphoma, metastatic MCC	2017	Phase I/II, open label, single arm, multicenter	40	16 children aged 2-12 y and 24 adolescents aged 12-18 y	No	NA	NA
Nilotinib	Ph+ CML in the chronic phase	2018	Phase II, open label, single arm, multicenter	59	13 (2-17)	No	NA	NA

(continued)

Table 1. (continued)

Medication	Indication	Pediatric approval, y	Phase and trial design	Sample size, No.	Study participants' age, median (range), y	PRO data reported?	PRO/COA measures	PRO endpoints included in labeling?
Emapalumab	Primary HLH	2018	Phase II/III, open label, single arm, multicenter	61	1 (1 mo to 13 y)	No	NA	NA
Larotrectinib	Advanced solid or primary CNS tumors	2018	Phase I/II, open label, single arm, multicenter	31	5.3 (0.1-19.9)	Yes	PedsQL Infant Scale, PedsQL 4.0 Generic Core, Wong-Baker Faces Scale	Not included
Selumetinib	Neurofibromatosis type 1 and inoperable plexiform neurofibromas	2020	Phase I/II, open label, single arm, multicenter	50	10.2 (3.5-17.4)	Yes	NRS-11, PII, Pain Medication Survey, PedsQL 4.0 Generic Core Scale, DVQ, PROMIS–Mobility and Upper Extremity, QOL background form, 6-min walk test	Not included

[a]ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; B-ALL = B-cell acute lymphoblastic leukemia; BPI-SF = Brief Pain Inventory–Short Form; cHL = classic Hodgkin lymphoma; CML = chronic myeloid leukemia; CNS = central nervous system; COA = clinical outcome assessment; DVQ = Dysfunctional Voiding Questionnaire; HLH = hemophagocytic lymphohistiocytosis; MCC = Merkel cell carcinoma; MSI-H = microsatellite instability high; NA = not applicable; NRS = numeric rating scale; PedsQL = Pediatric Quality of Life Inventory; Ph+ = Philadelphia chromosome positive; PRO = patient-reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System; QOL = quality of life; SEGA = subependymal giant cell astrocytoma; T-ALL = T-cell acute lymphoblastic leukemia; T-LBL = T-cell lymphoblastic lymphoma; TCS = tuberous sclerosis complex.

interactions with the FDA and obtain feedback from the relevant FDA review division on appropriate research design and any applicable regulatory requirements. The OCE communicates its PRO-related recommendations with investigators early in the drug-development process through various mechanisms, such as proposed pediatric study request negotiations, written requests, and preinvestigational new drug meetings. Considerations to improve the likelihood of PRO data being incorporated into FDA labeling include a clear research objective, with a corresponding prospective statistical analysis plan; low levels of missing data; and use of PRO instruments that are well defined and reliable. Advancements in study design, training of investigators and study personnel, statistical methods, and instrument selection can drastically improve PRO data quality in pediatric cancer registration trials and thereby enhance interpretability and enable incorporation of PRO data in product labeling.

Our findings highlight a noteworthy gap in PRO research across pediatric oncology trials intended for product registration, but it is important to acknowledge that challenges to evaluating PROs are inherent in pediatric patient populations, such as the time and logistics involved and unanswered questions that remain concerning study design. For example, how should we handle discrepancies between clinician or observer report vs patient self-report? Which pediatric PRO measures have been translated into multiple languages and validated across different cultural and geographic contexts—an important consideration for global clinical trials? Would incorporating PRO assessments increase the burden of clinical trial participation for children and their caregivers and potentially affect trial recruitment or retention? It is notable, however, that numerous studies have repeatedly shown willingness among children and their caregivers to self-report their subjective treatment experiences (>80% enrollment rates and high retention over time) (18,19). Although challenges exist, it is feasible and important to begin including the child's perspective in pediatric oncology drug development.

Core Clinical Outcomes in Oncology Trials and Considerations for Instrument Selection

The OCE's approach to measuring symptoms and function in cancer trials focuses on 4 well-defined core concepts that are proximal to a therapy's effects on patients and their disease: disease-related symptoms, physical functioning, symptomatic AEs, and overall side effect impact on the patient (20). Our review found, however, that the most commonly used PRO instrument in pediatric cancer registration trials was the PedsQL Generic Core Scale. Generic measures, such as PedsQL and EQ-5D-Y/3L, are useful when evaluating broad, multidomain concepts such as health-related QOL because they include items regarding patients' psychosocial well-being. Although questions that address social and family status are important to patients and caregivers and contribute to health-related QOL, these concepts are distal from the effect of the drug on the patient and the patient's disease. They can also be affected by many non–drug-related factors. Therefore, in the regulatory context, it is recommended that investigators select PRO instruments that focus on physical functioning, disease symptoms, and symptomatic side effects.

A challenge unique to pediatrics is balancing the use of validated patient- and caregiver-reported versions of instruments when they both exist. The incorporation of fit for purpose and carefully collected observer-reported outcome assessments provides an opportunity to evaluate symptoms and function in even the youngest children. To be able to report reliably as observers, caregivers should be cognizant of the patient's disease experience, which requires that they spend sufficient time with the patient to accurately reflect the patient's observation. Critically, caregiver responses need to be limited to *observable* outcomes (13). Recent research shows that where pediatric self-report is possible, it should be elicited directly from the pediatric patient with cancer as opposed to the caregiver because of limited agreement between child self-report and caregiver responses (9). Mack et al. (9) found that caregivers tended to overestimate symptom burden and underestimate function. It is possible that caregiver report of symptoms is influenced not just by the child's experience but by the caregiver's own health state and expectations for illness and symptom trajectory (21). Several studies have shown that more patient-caregiver agreement is seen in observable domains, such as mobility, rather than less visible domains, such as emotional state (9,22,23). Therefore, the FDA encourages limiting caregiver responses to observer-reported outcomes—those events or behaviors that can be observed in patients who cannot reliably respond for themselves (eg, infant patients) (13).

Another important consideration when selecting a PRO instrument is to ensure that the proposed instrument is fit for purpose for the target patient population (24). In our review, we noted that sponsor-submitted documents seldom included strong evidence demonstrating the validity, reliability, and responsiveness of the selected PRO instrument within the target patient population. For instance, it is concerning that 1 of the trials included in this review used the Brief Pain Inventory–Short Form in adolescents, despite the fact that it has not been validated in this patient population. Trials that recruit both adult and pediatric patients need to give thoughtful consideration to instrument selection and consider a priori subgroup analyses that are adequately powered. Although few PRO instruments span from childhood to adulthood, investigators can consider using PRO measurement systems that include both childhood and adulthood forms, such as the Patient-Reported Outcomes Measurement Information System or PRO-CTCAE, when recruiting patients from across the life span.

For instruments that are yet to be well studied within the target patient population, investigators can use qualitative studies to establish the validity and reliability of the instrument. Qualitative studies can also aid with item selection when item banks or item libraries are used (25). Similarly, cognitive interviews with patients and caregivers can help establish whether the proposed instrument's recall period, response scale, reading level, and use of health-related vocabulary are appropriate for the target patient population (25). For instance, it is notable that the trials included in our review generally used the standard version of the PedsQL, which has a 30-day recall period, rather than the acute version, which has a 7-day recall period. PRO instruments that require patients to rely on memory over a lengthy recall period are likely to increase measurement error (13). Items with shorter recall periods or items that ask patients to describe their current/recent state are generally preferred. If detailed recollection of experience over a longer period of time is necessary, we recommend that appropriate methods and techniques be employed to enhance the validity and reliability of retrospectively reported data (eg, ask patients to respond based on their worst [or best] experience over the recall period, or use a diary for data collection) (13).

Ultimately, PRO instruments will need to be selected and applied based on the trial objective and within the context of the study population in terms of age, cancer type, current disease status, and disease clinical course/natural history. As a case example, consider a pedagogical product application for the treatment of a solid tumor where pain—a disease symptom—is of considerable concern. Pain is unobservable; therefore, investigators would need to rely more heavily on the child's self-report. If the sponsor were to seek approval for an efficacy endpoint related to pain palliation based on a PRO measure, then questions for trial investigators to consider would include whether the proposed PRO instrument has an adequate evidence base supporting its use in the study's target patient population or whether the investigators would need to generate this evidence for themselves first. Is the proposed instrument appropriate for the age, literacy level, and cognitive abilities of the study population? Does the child understand and interpret the items and response scale as intended? Have the measurement properties of the instrument been well evaluated in the context of the target patient population? Are any reductions in patient-reported pain resulting from tumor shrinkage or better pain management through use of analgesics? Notably, none of the trials included in this review captured data on concomitant use of analgesics. Such data can be supportive and useful in understanding change in patients' pain trajectories from baseline (26), but it is important to recognize that information on coanalgesics can be difficult to interpret given that not all modifications to pain regimens are associated with a corresponding change in actual pain levels.

Considerations Related to Study Design and Statistical Methods

Single-arm trials are common in pediatric oncology drug development because of ethical concerns around placing patients on placebo or wait-listing them in crossover study designs. In fact, only 5 (29%) of the 17 products reviewed were approved based on randomized trials, and all 4 applications that included PROs had a single-arm study design. The absence of a control arm complicates our ability to draw meaningful conclusions from PRO data, particularly with respect to efficacy, given concerns about an overestimation of benefit when patients are aware of treatment assignment (13). There is a need to characterize the existence and magnitude of bias in open-label cancer trials (27). Work in adult patients with cancer suggests that although open-label bias may have a potential effect on PRO assessment completion rates (12), evidence showing that knowledge of treatment assignment has a large effect on PRO responses in the oncology setting is currently limited (27). Concerns about interpreting PRO findings from single-arm studies can be addressed by using prespecified and appropriate thresholds for clinically meaningful within-patient score change in the concepts of interest. In the case of pain assessments, for example, the FDA has traditionally accepted a 30% reduction and 3-point change on the 11-point numeric rating scale (26). The threshold, however, for clinically meaningful within-patient score change for most other concepts and PRO instruments in pediatric oncology largely remains unknown.

The FDA recommends use of anchor-based methods to develop thresholds for meaningful within-patient score change (13). These methods explore the associations between the targeted concept of the PRO instrument and the concept measured by external anchors. For example, a patient global impression rating scale can be used as an external anchor to interpret clinically meaningful within-patient score change (13), but further research and consensus are needed on the reliability and appropriate use of patient global impression rating scales within pediatric populations (28) because it has been found that correlations between PRO measures and corresponding anchors are often below 0.3—the recommended lower bound for correlation between a scale and its anchor (28,29). Questions also exist concerning whether younger pediatric patients can fully understand and interpret how to respond to a patient global impression rating scale. For this population, other methods may need to be explored to complement anchor-based methods or when anchor-based methods are not feasible (ie, when no adequate anchors are available or when trials have small sample sizes). For instance, patients can be queried during cognitive interviews, exit interviews, or surveys to help inform the threshold of meaningful within-patient score change. Ultimately, however, investigators may need to consider multiple anchors and triangulate results to arrive at an appropriate threshold.

Small sample sizes are inevitable in pediatric oncology trials. The added caution and procedural complications of enrolling and conducting research in pediatric populations further challenge the use of PRO measures in children. The majority of trials included in this review had fewer than 100 study participants per trial, which limits our ability to generalize and interpret study findings and may also result in inadequate power to detect statistically significant differences in PROs, especially if the endpoint is categorical (eg, responder vs nonresponder). Nevertheless, investigators still have the opportunity to collect PRO data in smaller studies through repeated measures and perform in-depth and descriptive analyses. Smaller sample sizes allow for the analysis of individual patient trajectories—for instance, through the use of spaghetti plots for physical functioning, which are not useful in larger trials.

Our review also found that completion rates were not being reported as standard practice in clinical study reports submitted by sponsors, although the OCE now often requests this information from sponsors that do not provide it voluntarily. Completion rates are an important quality indicator. When patients who are scheduled to complete a PRO assessment miss one, it is often unknown whether those patients are experiencing more disease symptoms or toxicity and as a result unable to complete their PRO assessments. This gap could mean that the study systematically missed patients who were experiencing higher levels of toxicity. PRO responses are therefore not missing at random. Explicit communication of completion rates can help address concerns about missing data and related biases. Every effort must be made to prevent missing PRO data through the use of reminders and explanations to patients and families of why continued participation in PRO assessments is important to trial outcomes. If PRO assessments are incomplete for a given patient, then documenting and reporting the specific reasons for the missing data (eg, administrative error, patient felt too ill, study coordinator thought the patient was too ill) can help determine appropriate statistical methods to address the dominant reason for missing data.

Finally, as a result of decreasing numbers of on-treatment study participants, a phenomenon common in oncology trials across patients of all ages, we observed a decline in the number of PRO assessments completed over the course of each trial. Sponsors need to determine, a priori, whether their target population includes only patients who remain on treatment or all patients randomized/assigned to treatment. If the latter, thoughtful decisions must be made as to whether and when to

collect data from patients who no longer remain on therapy and for what duration these data will be collected, especially if a long trial is anticipated. Continued PRO assessments are particularly relevant in pediatric oncology, given the longer period of survivorship these patients experience. Decisions on the continuation, frequency, and interval of PRO assessment should take patient/caregiver burden into consideration and address a well-defined study objective.

Future Directions: Using PROs to Inform Safety and Tolerability

Through efforts sustained over several years, the FDA has encouraged the use of PROs in cancer registration trials by establishing the OCE PFDD initiative (1), Project Patient Voice (30), publication of PFDD guidance documents (31), journal publications indicating our perspectives on the utility of PROs in drug development (11,32–34), and numerous workshops on this subject. The OCE is taking a proactive approach to ensure that pediatric patients are included in the PFDD initiative through pediatric oncology–specific PRO workshops, stakeholder meetings, and publications. In the near term, we have an opportunity to use PROs to complement our understanding of safety and tolerability in pediatric oncology drug development. As reported in our results, symptomatic AEs in pediatric cancer registration trials have traditionally been characterized using clinician-reported CTCAE and have *not* been complemented with patients' self-report. Recently, the National Cancer Institute developed and validated a pediatric version of the PRO-CTCAE, offering a novel opportunity to elevate the child's voice in drug-development efforts going forward. The Pediatric PRO-CTCAE enables self-report of symptomatic AEs by children and adolescents aged 7-17 years. A corresponding caregiver version has also been designed for reporting in children younger than 7 years of age (35). This 130-item library represents 62 symptomatic toxicities drawn from the CTCAE (10,18). The items evaluate the presence or absence of symptoms and their attributes, such as frequency, severity, and interference (36). The FDA officially launched Project Patient Voice in June 2020 with the purpose of communicating patient-reported symptom data from cancer clinical trials to the public. This platform is intended for use by patients and caregivers along with their health care providers during discussions about treatment options (30). The advent of the Pediatric PRO-CTCAE provides a unique opportunity for potential inclusion of pediatric patients in Project Patient Voice, as well.

Pediatric drug development has gained ground over recent decades through passage of legislation such as the Best Pharmaceuticals for Children Act, Pediatric Research Equity Act, and Research to Accelerate Cures and Equity Act, all of which were passed specifically to benefit children. The 21st Century Cures Act and the FDA's PFDD initiative are intended to benefit patients of all ages, including children. Our study has identified an important opportunity to expand the use of PROs in commercial pediatric cancer clinical trials, particularly to inform symptomatic side effects from the patient perspective. Drug development stakeholders are encouraged to work together to advance the use of PROs within pediatric oncology and thereby provide a more comprehensive assessment of the safety and tolerability profile of cancer therapeutics. One near-term opportunity is to advance the use of PRO measures such as the Pediatric PRO-CTCAE to inform the incidence and impact of symptomatic side effects in pediatric oncology patients. The FDA's OCE has made great strides in advancing PROs in adult oncology trials. It is now time to proactively approach incorporating PROs into pediatric oncology drug development. We cannot afford to leave children behind: They deserve better.

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Data Availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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