

The First Step to Integrating the Child's Voice in Adverse Event Reporting in Oncology Trials: A Content Validation Study Among Pediatric Oncology Clinicians

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Purpose. Children with cancer experience significant toxicities while undergoing treatment. Documentation of adverse events (AEs) in clinical trials is mandated by federal agencies. Although many AEs are subjective, the current standard is clinician reporting. Our long-term goal is to create and validate a self-report measure of subjective AEs for children aged 7 years and older that will inform AE reporting for the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). This content validation study aimed to identify which of the AEs in the current CTCAE should be included in a pediatric self-report measure. **Methods.** We sought expert panel review and consensus among 187 pediatric clinicians from seven Children's Oncology Group institutions to determine which of the 790 AEs are amenable to child self-report.

Two survey iterations were used to identify suitable AEs, and clinician agreement estimated by the content-validity ratio (CVR) was assessed. **Results.** Response rates for surveys 1 and 2 were 72% and 67%, respectively. After the surveys, 64 CTCAE terms met the criteria of being subjective, relevant for use in pediatric cancer trials, and amenable to self-report by a child. The most frequent reasons for removal of CTCAE terms were that they relied on laboratory or clinical measures or were not applicable to children. **Conclusion.** The 64 CTCAE terms will be translated into child-friendly terms as the basis of the child-report toxicity measure. Ultimately, systematic collection of these data will improve care by enhancing the accuracy and completeness of treatment toxicity reports for childhood cancer. *Pediatr Blood Cancer* © 2013 Wiley Periodicals, Inc.

Key words: adverse events; cancer; clinical trials; patient-reported outcomes; pediatric; validity

INTRODUCTION

In the US, cancer will be diagnosed in approximately 12,060 children between the ages of 0 and 14 years during 2012 [1], and more than 60% of children with cancer will participate in clinical trials [2,3]. The federal government mandates that all trials report adverse events (AEs) [4]. The standard lexicon for grading and reporting AEs in oncology clinical trials is the Common Terminology Criteria for Adverse Events (CTCAE) developed by the National Cancer Institute (NCI). The CTCAE (version 4.03; June 14, 2010) contains 790 AE terms organized into 26 system organ classes (e.g., allergy/immunology, auditory/ear, blood/bone marrow, cardiac, endocrine, gastrointestinal) [4], with AEs graded from 1 (mild) to 5 (death related to AE).

Oncology clinicians identify and grade all AEs, an approach that systematically under-reports the prevalence and severity of subjective AEs such as pain, fatigue, insomnia, depression, anxiety, and nausea in adult patients with cancer [5–9]. Therefore, the NCI funded an initiative to design and validate a patient-reported outcomes (PRO) version of the CTCAE [10]; the resulting PRO-CTCAE measure is limited to adults 21 years and older.

Children with cancer also experience a significant burden of subjective AEs, including decrements in physical, mental, and social health domains as well as disruptions in primary and secondary education [11–20]. Furthermore, studies comparing child, parent, and clinician symptom ratings show that clinicians and caregivers are poor at recognizing the presence or intensity of children's symptoms [21–24]. Directly incorporating the child's perspective into the grading of subjective AEs will ensure the collection of accurate and complete data about treatment toxicities. Therefore, our goal is to design and validate a pediatric version of the PRO-CTCAE measure to account for the unique capabilities, challenges, needs, preferences, and experiences of children with cancer.

We performed a content validity study to identify AEs listed in the CTCAE that may be amenable to self-report by children with cancer (ages 7 years or older) as a first step towards creating a pediatric version of the PRO-CTCAE measure. We wanted to

ensure that all CTCAE terms relevant for children were included in, and terms without relevance for children excluded from, the development of the pediatric version of the PRO-CTCAE measure. A secondary study aim was to identify "core" subjective AEs that are prevalent in children across a range of cancer (and treatment) types and are therefore of high clinical priority when seeking to measure treatment impact.

METHODS

Rationale

Children as young as 7 years who are in treatment for cancer can reliably and validly report their symptom and quality-of-life

Additional supporting information may be found in the online version of this article.

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experiences using questionnaires [25–32]. Because our long-term goal is to develop a questionnaire that a child with cancer can respond to without help from a caregiver or interviewer, our first step in designing a pediatric version of the PRO-CTCAE was to determine which of the 790 AE terms would be most applicable and reportable by this age group. Because the CTCAE are written in medical terms and require in-depth clinical knowledge to determine whether a subjective component for grading the AEs exists, only experts in pediatric oncology care were involved in this initial stage of selecting CTCAE terms.

Approach

We used a modified Delphi process based on the RAND/UCLA Appropriateness Method [33], a method accepted as providing content-valid results [34]. Our approach is a consensus technique that involves the participation of experts and has four distinguishing features: anonymity, iteration (two survey rounds), controlled feedback (i.e., the results of each survey are analyzed separately and reported back to experts), and statistical group response (i.e., distribution of agreement among the experts) [33].

First-Iteration Survey Design

The 790 CTCAE terms were considered to be too many to ask clinicians to review in a formal survey. A four-member panel of pediatric clinical and research experts reviewed the full list of CTCAE terms and removed terms that were graded based on laboratory-based measures. The panel was composed of a pediatric oncologist with 7 years of experience, a pediatric registered nurse with 5 years of experience, a pediatric oncology registered nurse with 26 years of experience, and a developmental pediatric psychologist with 16 years of experience in oncology. The panelists independently reviewed all CTCAE terms and then met as a group to review their selections. Consensus for including or excluding a term was necessary to move to the next step. The panel reached initial consensus on removing 528 of the 790 terms that were laboratory-based measures, and consensus about 22 disputed items was subsequently achieved. Thus, 262 CTCAE terms were selected for the first-iteration survey.

First-Iteration Survey Distribution and Analysis

After this study was approved or ruled exempt from review by the institutional review boards, pediatric clinicians and researchers from seven Children's Oncology Group (COG) sites were invited to participate in our survey; the authors did not participate in the survey. First, the authors identified a total of 187 clinicians, including physicians, nurse practitioners, nurses, and physician assistants, who had 2 or more years of experience in child and adolescent cancer care. Each received a letter inviting their participation in the study with a \$5 gift card. The letter described the purpose and value of the study, the details of the two survey requests that would be sent, the anonymity of the survey, and the voluntary nature of participation. Next, the survey link was e-mailed within 7 days of the hardcopy invitation being distributed. Finally, the invitees received weekly e-mail reminders during a 3-week period.

The survey, administered using Research Electronic Data Capture (REDCap; v.4.14.3, 2012, Vanderbilt University) software, included instructions on the first screen re-emphasizing the study

purpose, our appreciation for the respondents' time, the anonymity of the survey, and that all participants' data would be aggregated. For each CTCAE term, clinicians answered the questions shown in the Supplemental Appendix. To reduce respondent burden and keep the survey under 30 min, two forms of the survey (Forms A and B) were created, with 131 CTCAE terms randomly assigned to each form; respondents were randomly assigned to either form. Clinicians also responded to demographic questions about their training, gender, and years of experience.

We created detailed summaries of responses to each CTCAE term in survey 1, including the number of "yes" votes and the content-validity ratio (CVR). Developed by Lawshe, the CVR gauges agreement among raters and is calculated as $CVR = (n_{yes} - N/2)/(N/2)$, where n_{yes} indicates the number of raters indicating "yes" for the CTCAE term and N indicates the total number of raters [35]. CVR values range from +1 to -1, with positive values meaning that at least half of the raters rated the item as "yes." The minimum CVR value necessary to ensure that agreement is unlikely to be due to chance varies by the number of raters. For example, when $N = 10$, the minimum CVR value should be at least 0.62 and the corresponding percentage of rating "yes" should be at least 81% for an item to ensure true agreement; however, when $N = 40$, CVR should be at least 0.29 and the percentage rating "yes" should be at least 65% to ensure agreement. Although the study included more than 40 raters, we chose the conservative cutoff CVR value of 0.30 (equivalent to at least 65% of the raters indicating "yes") for the CTCAE term to minimize the likelihood of evaluating chance agreements.

Although statistical analyses were conducted and *a priori* criteria were applied, decisions to keep or remove a CTCAE term were not made without considering the content of the AE. AEs below the threshold for removal were carefully reviewed by the study team to ensure that no mistake was made on the survey (e.g., spelling mistake) and that there was no misunderstanding of how the AE was defined according to the CTCAE.

Second-Iteration Survey Design

With guidance from the results of survey 1, the oncology clinical members of the study team (P.H., D.R.F., M.C.H., J.W., J.B., L.S., D.T., S.J.) evaluated the remaining CTCAE terms, specifically their clinical observability (i.e., is it likely to be identified by the clinician even if the child isn't asked?), clinical importance, transient or durable nature, relevance for children with cancer, and presence on the adult version of the PRO-CTCAE. This review was completed independently by each member and then responses were aggregated to select terms for the second clinician survey. AEs were removed if judged to be clinically observable or irrelevant for children. Also, investigators identified CTCAE terms that were similar to each other and selected one of the terms to be removed. AEs that were retained (considered subjective) and those that raters disagreed upon were included in the second clinician survey.

Second-Iteration Survey Distribution and Analysis

Six respondents to survey 1 were no longer employed at participating sites at the time of survey 2; the remaining 181 clinical reviewers from survey 1 were asked to participate in survey 2. Procedures and analyses used for survey 2 were similar to those used for survey 1 except that all respondents received the

same survey form. The survey 2 instructions and questions are provided in the Supplemental Appendix. The questions in survey 2 sought to achieve further consensus on the subjective AEs and to identify core AEs, that is, those that are prevalent in children with different cancer (and treatment) types and are relevant for capturing clinically important symptomatology in children and adolescents with cancer. Qualtrics survey software was used for survey 2. Analyses were conducted by calculating CVR as in survey 1. Study investigators reviewed the final set of CTCAE terms, focusing on which terms were clinically important, commonly experienced by children with cancer, and best reported by patients as opposed to by caregiver-proxies or clinicians.

RESULTS

First-Iteration Survey Analysis

A total of 135 of 187 clinicians (72%) responded to the first survey, with 66 completing Form A and 69 completing Form B (Table I). Of the 262 CTCAE terms reviewed, 90 had a CVR value below 0.30 and had corresponding agreement levels among clinicians that were less than 65% in regard to a child or adolescent being able to report on the AE. The study team carefully reviewed all 90 terms and retained 3 of them (arthralgia, CVR = 0.27, 63.6% agreement; myalgia, CVR = 0.27, 63.6% agreement; and peripheral sensory neuropathy, CVR = 0.29,

64.7% agreement) These AEs were considered to be common and potentially serious toxicities that might be best captured through direct child report and are included on the adult version of the PRO-CTCAE.

Second-Iteration Survey Design

Clinical members of the study team reviewed the remaining 175 CTCAE terms, taking into account the subjective nature of the AEs and their relevance for children with cancer. The following CTCAE terms were removed: 36 AEs judged to be best assessed by clinical observation (e.g., injection site reaction, tooth discoloration), 11 AEs related to reproduction or sexual events (e.g., unintended pregnancy, dyspareunia, erectile dysfunction), and three AEs deemed to be rare and low-priority events (floaters, photophobia, body odor). We also removed 30 CTCAE terms that measured body site-specific pain (e.g., lip pain, pharyngolaryngeal pain, gallbladder pain), retaining only abdominal pain, urinary tract pain, headache, and general pain. Additionally, 16 CTCAE terms were removed due to their similarity to other CTCAE terms. For example, vertigo was removed due to similarity to dizziness; bloating was similar to abdominal distension, and purpura was similar to bruising. After review, 79 CTCAE terms were retained for the second survey, including those perceived to be subjective, those investigators disagreed about, and those included on the adult PRO-CTCAE.

TABLE I. Characteristics of Participants in Clinician Surveys

Variable	Survey 1 (form A)	Survey 1 (form B)	Survey 1 total	Survey 2 total
# Participated in survey	66	69	135	121
Professional degree (could select ≥1 degree)				
Physician	31 (47%)	38 (55%)	69 (51%)	61 (51%)
Physician assistant	2 (3%)	2 (3%)	4 (3%)	7 (6%)
Nurse practitioner	15 (23%)	16 (23%)	31 (23%)	27 (23%)
Registered nurse	10 (15%)	15 (22%)	25 (19%)	28 (23%)
PhD	9 (14%)	4 (6%)	13 (10%)	2 (2%)
Years in pediatric oncology				
2–4	13 (20%)	16 (23%)	29 (21%)	16 (13%)
5–8	16 (24%)	15 (22%)	31 (23%)	30 (25%)
9–12	14 (21%)	10 (14%)	24 (18%)	24 (20%)
13–15	10 (15%)	8 (12%)	18 (13%)	12 (10%)
16–20	5 (8%)	8 (12%)	13 (10%)	16 (13%)
21–25	4 (6%)	9 (13%)	13 (10%)	14 (12%)
26+	4 (6%)	3 (4%)	7 (5%)	9 (7%)
Gender				
Female	48 (73%)	51 (74%)	99 (73%)	85 (71%)
Male	18 (27%)	18 (26%)	36 (27%)	34 (29%)
Children's Oncology Group member				
Yes	53 (80%)	56 (81%)	109 (81%)	101 (84%)
No	13 (20%)	13 (19%)	26 (19%)	17 (14%)
Unsure				2 (2%)
Site				
Children's Hospital Los Angeles	16 (24%)	20 (29%)	36 (27%)	33 (27%)
Children's National Medical Center	14 (21%)	14 (20%)	28 (21%)	30 (25%)
DFCI/Boston Children's Hospital	9 (14%)	9 (13%)	18 (13%)	14 (12%)
Palmetto Health Children's Hospital	4 (6%)	3 (4%)	7 (5%)	7 (6%)
St. Jude Children's Hospital	11 (17%)	11 (16%)	22 (16%)	14 (12%)
University of Minnesota	4 (6%)	3 (4%)	7 (5%)	9 (7%)
UNC/NC Cancer Hospital	8 (12%)	9 (13%)	17 (13%)	14 (12%)

DFCI, Dana-Farber Cancer Institute; UNC, University of North Carolina; NC, North Carolina.

Second-Iteration Survey Analysis

A total of 121 clinicians (67%) responded to survey 2 (Table I). Clinicians generally agreed about whether information about the CTCAE should be provided by only the child or by the child and caregiver-proxy. However, four terms had a CVR less than 0.30 (irritability, myalgia, memory impairment, and confusion); myalgia and memory impairment were retained because they are in the adult version of the PRO-CTCAE.

After a final review of the results from the second survey, investigators removed six AEs judged to be observable in the clinic: gait disturbance, nasal congestion, flushing, oral hemorrhage, allergic reaction, and allergic rhinitis. The term

hallucination was removed because it is likely difficult for younger children to report, may have a different meaning for children (distinguishing for example between imaginary friends and a sensory experience that does not have external stimuli) than adults, and is not included on the adult PRO-CTCAE. Menorrhagia and irregular menstruation were removed because they are not applicable to young children. Four other terms were removed because they were similar to other terms: dysmenorrhea (related to abdominal pain), somnolence (related to fatigue), malaise (related to generalized muscle weakness), and flu-like symptoms (related to fever, fatigue, anorexia, and other AEs). Figure 1 provides a flow chart detailing how the 790 CTCAE terms were reduced to 64 terms deemed amenable to self-report by children.

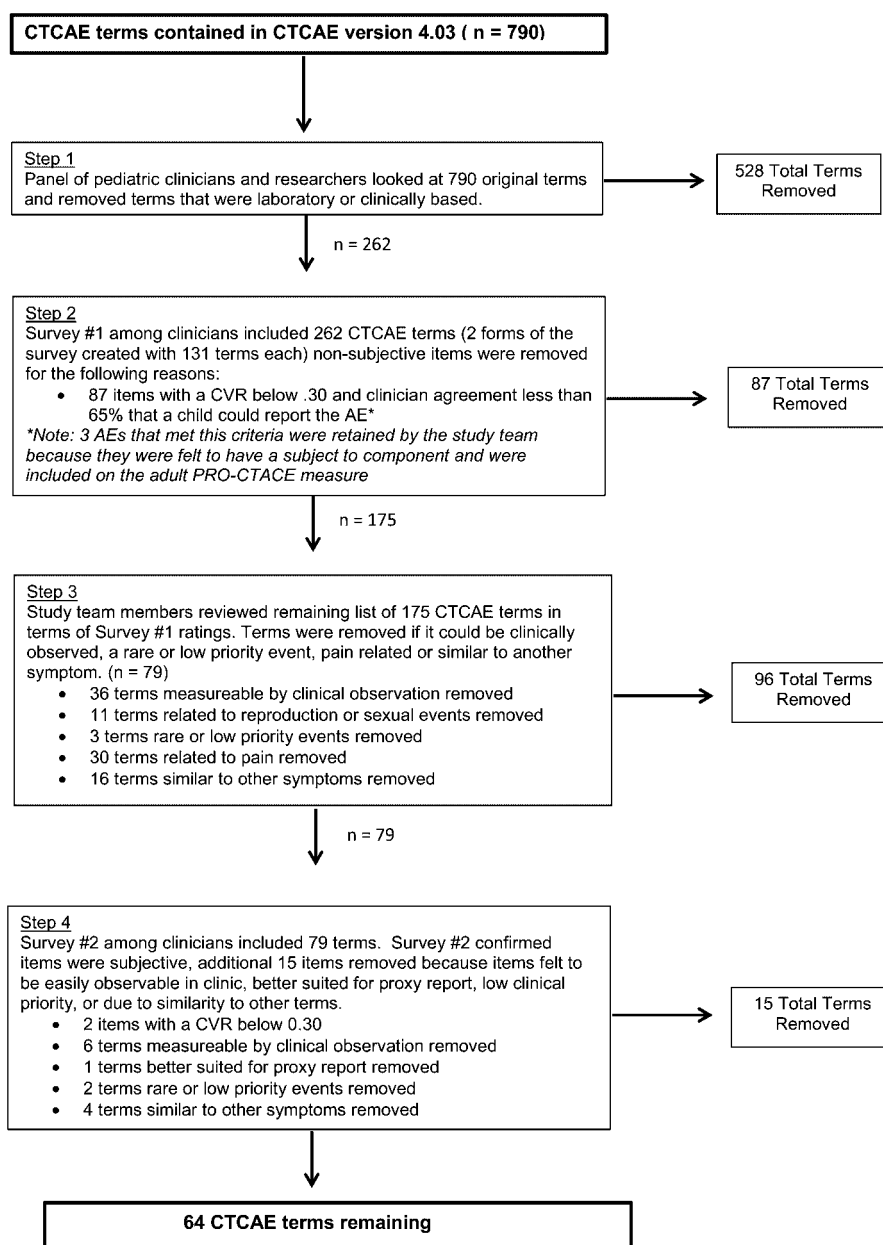


Fig. 1. Consort flowchart detailing selection of Common Terminology Criteria for Adverse Events (CTCAE) terms that are amenable to self-report by children aged 7 years or older.

TABLE II. Final 64 Common Terminology Criteria for Adverse Events (CTCAE) Terms Selected for Translation to the Pediatric Version of the PRO-CTCAE

Selected "core" CTCAE terms	
Abdominal pain	Fever
Anorexia	Headache
Anxiety	Insomnia
Constipation	Mucositis oral
Cough	Nausea
Depression	Pain
Diarrhea	Peripheral sensory neuropathy
Fatigue	Vomiting
Other selected CTCAE terms	
Abdominal distension	Hot flashes
Alopecia	Hyperhidrosis
Arthralgia	Memory impairment
Blurred vision	Myalgia
Bruising	Palpitations
Chills	Photosensitivity
Concentration impairment	Pruritus
Dizziness	Rash acneiform
Dry eye	Restlessness
Dry mouth	Skin ulceration
Dry skin	Sneezing
Dysgeusia	Sore throat
Dyspepsia	Suicidal ideation
Dysphagia	Tinnitus
Dyspnea	Urinary frequency
Edema limbs	Urinary incontinence
Epistaxis	Urinary tract pain
Fall	Urinary urgency
Fecal incontinence	Urine discoloration
Flashing lights	Urticaria
Flatulence	Vaginal discharge
Generalized muscle weakness	Voice alteration
Hiccups	Watering eyes
Hoarseness	Wheezing

PRO-CTCAE, Patient-Reported Outcomes version of Common Terminology Criteria for Adverse Events.

Table II lists the final 64 CTCAE terms selected and the 16 CTCAE terms selected by the investigators as being core AEs that should be routinely assessed among children participating in oncology trials. All core terms received 65% or higher endorsement by the clinicians in the second survey.

DISCUSSION

This content validity study provides the foundation for creating a pediatric version of the PRO-CTCAE measure, reducing the 790 CTCAE items to 64 essential AE terms, including 16 core terms. The terms may now be translated into child-friendly language that will ultimately comprise the items for the pediatric PRO-CTCAE measure; the psychometric properties of the pediatric PRO-CTCAE can then be evaluated.

Our decision to include a broad group of experienced clinicians who represent the roles involved in completing the CTCAE or who provide the clinical assessments from which the AEs are

extracted and reported to the NCI is consistent with recommended guidelines for conducting Delphi studies and seeking consensus by using multidisciplinary panels to better reflect the variety of specialties involved in child care and research [36,37]. Additionally, the clinicians represented seven COG sites, that were diverse in terms of size, location, and racial/ethnic composition of their patient populations served. These considerations increase the likelihood that the COG will adopt our pediatric measure in its trials [36].

The selection of CTCAE terms was, in part, guided by the intent to make the pediatric version as efficient and child-friendly as possible. For example, we combined many of the redundant pain-related questions because our goal is not to ask a child about pain on every part of his/her body but rather to screen for pain and expect the clinician to follow-up about pain location and history. We also removed AE terms that patients may not differentiate from other AE terms, such as "dizziness" and "vertigo." Although great care was taken to provide a rigorous methodology for this content validity study, this essential first step is part of a planned larger initiative to design the Pediatric PRO-CTCAE measure. CTCAE terms retained as a result of this study could ultimately be removed if the validation study finds that patient reports do not add information helpful to clinicians or investigators or if the term cannot be translated into acceptable child-appropriate terms.

Our approach was similar to that used to design the adult version of the PRO-CTCAE measure. Although our process involved only pediatric clinicians, 56 of the 64 CTCAE terms selected are also included in the adult PRO-CTCAE measure. Similarity across the pediatric and adult versions of the PRO-CTCAE could facilitate comparisons of study results among trials that enroll younger children (who may answer the pediatric version) and older adolescents or young adults (who may take the adult version). The eight terms unique to the pediatric list of AEs are dry eye, fever, fall, generalized muscle weakness, restlessness, sneezing, sore throat, and suicidal ideation. The 21 CTCAE items on the adult version that were not a priority for the pediatric population included measures of sexual functioning and those of skin and nail changes that could be assessed by clinicians during a physical exam.

A potential limitation of this study is that children with cancer and their caregivers were not included at this early point in the process, because of the highly technical medical jargon used in the CTCAE, and the high number of items. Despite a liberal inclusion selection process, the clinician ratings may have resulted in removal of a term that children and parents would have deemed important. This risk will be addressed in the future steps of developing the pediatric PRO-CTCAE, which will include direct input from children and adolescents with cancer and their parents. As the planned validation process is furthered, comparisons of the pediatric PRO-CTCAE version with child reports of symptoms and quality of life will be completed and expert input from psychosocial clinicians and behavioral scientists along with clinicians will enhance the validity of the measure and value of the data.

The next step in creating a pediatric PRO-CTCAE is to translate the medical jargon into language likely to be understood by children as young as 7 years and to design an initial draft of the questionnaire. This step will involve reviewing the literature and existing symptom-related questionnaires to find appropriate

language for the directions that will guide patients in responding to the items on the pediatric PRO-CTCAE and identify response formats readily understood by children. English and Spanish versions will be designed and evaluated in parallel. Cognitive interviews will be conducted with children with cancer and with their parents to establish and refine the questionnaires until they are deemed to be clear, understandable, and relevant for capturing AEs. A longitudinal study will follow to evaluate the psychometric properties of the pediatric PRO-CTCAE measures and the congruence among AE ratings reported by clinicians, children, and their caregiver-proxies. Future work will also evaluate the feasibility of collecting data on the pediatric PRO-CTCAE in oncology trials and the added value of the child-reported data for improving CTCAE grading. Thus, as the pediatric PRO-CTCAE is developed, tested, and implemented, research will be increasingly informed by the child's subjective treatment experience, which is an important but currently under-represented parameter in evaluating and comparing treatment regimens for children with cancer.

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