Cognitive Interview-based Validation of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) in Adolescents with Cancer

Bryce B. Reeve, University of North Carolina
Molly McFatrich, University of North Carolina
Laura C. Pinheiro, University of North Carolina
David R. Freyer, Children's Hospital Los Angeles
Ethan M. Basch, University of North Carolina
Justin N. Baker, St. Jude Children's Research Hospital
Janice Squires Withycombe, Emory University
Lillian Sung, Hospital for Sick Children
Jennifer W. Mack, Dana-Farber Cancer Institute
Mia K. Waldron, Dana-Farber Cancer Institute

Only first 10 authors above; see publication for full author list.

Journal Title: Journal of Pain and Symptom Management
Volume: Volume 53, Number 4
Publisher: Elsevier: 12 months | 2017-04-01, Pages 759-766
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1016/j.jpainsymman.2016.11.006
Permanent URL: https://pid.emory.edu/ark:/25593/s8x5t

Final published version: http://dx.doi.org/10.1016/j.jpainsymman.2016.11.006

Copyright information:
© 2017 American Academy of Hospice and Palliative Medicine

Accessed November 1, 2019 12:51 AM EDT
Cognitive Interview-based Validation of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) in Adolescents with Cancer

Bryce B. Reeve, PhD1,2, Molly McFatrich, MPH1, Laura C. Pinheiro, MPH1,2, David R. Freyer, DO, MS3, Ethan M. Basch, MD, MSc1, Justin N. Baker, MD, FAAP, FAAHPM4, Janice S. Withycombe, PhD, RN, MN, CCRP5, Lillian Sung, MD, PhD6,7, Jennifer W. Mack, MD, MPH8, Mia K. Waldron, MSN-Ed, RN-BC, CPN9, Catriona Mowbray, PhD, BSN, RN, CPN10, Diana Palma, BS, CCRP3, and Pamela S. Hinds, PhD, RN, FAAN9,11

1Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA
2Department of Health Policy and Management, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA
3Children’s Center for Cancer and Blood Diseases, Children’s Hospital Los Angeles, Los Angeles, CA, USA
4Department of Oncology, Division of Quality of Life and Palliative Care; St. Jude Children’s Research Hospital, Memphis, TN, USA
5Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, GA, USA
6Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Canada
7Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, Canada
8Dana-Farber Cancer Institute, Boston, MA, USA
9Department of Nursing Research and Quality Outcomes, Children’s National Health System, Washington, DC, USA
10Department of Oncology, Children’s National Health System, Washington, DC, USA
11Department of Pediatrics, George Washington University, Washington, DC, USA

Abstract

Context—The National Cancer Institute created the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) to allow direct input on symptomatic AEs from adult patients in oncology trials.
**Objectives**—This study sought to determine the youngest age to complete the PRO-CTCAE, evaluated comprehension of PRO-CTCAE among adolescents, tested new items not currently in PRO-CTCAE, and tested a parent-proxy version.

**Methods**—From 7 pediatric cancer hospitals, 51 adolescents (13–20 years) receiving cancer treatment participated, along with 40 parent-proxies. We evaluated 55 AEs from the PRO-CTCAE library (97 questions) and 7 new AEs not in PRO-CTCAE that assess symptom frequency, severity, interference, or presence. Questions were distributed across 3 forms to reduce burden. Cognitive interviews with retrospective probing were completed in age groups of 13–15 and 16–20 year-olds. Proxies were interviewed independently.

**Results**—In general, the 16–20 year-olds and the parent-proxies were able to understand and complete the PRO-CTCAE and newly designed AE questions. Five PRO-CTCAE terms (bloating of the abdomen, anxiety, flashing lights in front of your eyes, hot flashes, bed sores) and the wording of the questions about AE severity were challenging for a few adolescents and proxies. The 13–15 year-olds had greater challenges completing the PRO-CTCAE.

**Conclusions**—This study extends use of the adult PRO-CTCAE for adolescents as young as 16 years, and proposes new questions for 7 new symptomatic AEs and a parent-proxy version of PRO-CTCAE. Additional testing of the new questions and alternative language for more challenging PRO-CTCAE items is recommended in adults.

**Keywords**

patient-reported outcomes; adverse events (AEs); cognitive interviews; cancer; adolescents

**Introduction**

Adverse events (AEs) are required for reporting in clinical trials, and are used for safety evaluation for drug approvals. In oncology trials, the standard lexicon for grading AEs is the United States (US) National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE is also used in industry-sponsored trials and drug labels for oncology products and is commonly employed by practitioners for toxicity assessment. The standard in clinical trials is for clinicians to identify, grade and report patient AEs. However, clinicians tend to underreport the number and severity of AEs compared to patients’ self-report.

In 2008, the NCI launched an initiative to design and validate a patient-reported outcomes version of the CTCAE (PRO-CTCAE) in order to integrate directly the patient’s voice in identifying and grading symptomatic AEs in oncology trials. Subsequently, the PRO-CTCAE was evaluated by cognitive interviews, and tested for validity in a longitudinal study in cancer patients. The US Food and Drug Administration (FDA) cited the benefits of using the PRO-CTCAE for assessing AEs to inform safety evaluation and drug labeling.

Although the evaluation of the PRO-CTCAE targeted adult cancer patients aged 18 years and older, patients 18–20 years old were under-represented; thus, the lower age to which the PRO-CTCAE measure may be validly used is unknown. The availability of a...
PRO-CTCAE measure is critical in this younger age group as many adolescents and young adults with cancer are known to have worse survival when compared to younger and older patients and are under-represented on clinical trials. Adolescents and young adults are also known to be at excess risk for treatment-related toxicity in comparison with other age groups. Thus, understanding their treatment experience is imperative.

In this in-depth cognitive interview study among adolescents (from 13–20 years), we evaluated their understanding of the PRO-CTCAE questions and their ability to provide valid responses in order to determine the lowest age at which an adolescent has sufficient understanding to use the adult PRO-CTCAE measure. We also evaluated a parent-proxy version of the PRO-CTCAE to determine whether parents of adolescents with cancer were able to understand and provide appropriate answers to the AE items. Cognitive interviewing is a necessary step in the design and validation of a PRO measure and recommended by the FDA. As the PRO-CTCAE is being widely used in clinical trials and observational studies, our study did not intend to modify the existing PRO-CTCAE measurement system, but to determine the minimal age that an adolescent is able to read and provide valid responses.

Methods

Participants and Setting

This study was part of a larger study funded by the NCI to design and evaluate a pediatric version of the PRO-CTCAE. Participants were recruited from seven geographically diverse pediatric hospitals: Children’s Hospital Los Angeles, Children’s National Health System (Washington, DC), The Hospital for Sick Children (Toronto, Ontario, Canada), Dana-Farber Cancer Institute and Boston Children’s Hospital, Palmetto Health Children’s Hospital (Columbia, SC), St. Jude Children’s Research Hospital (Memphis, TN), and the University of North Carolina. All sites received approval from their respective institutional review boards.

Adolescents ages 13–20 years in any phase of treatment for a diagnosis of cancer were eligible to participate. Thirteen years was selected as the lower age limit because adolescent vocabulary and cognitive abilities are more developed than younger counterparts. The adolescent’s parent/caregiver (proxy) must have been at least 18 years old. Participants have to speak English. Adults provided their own signed consent and adolescents younger than 18 years provided assent.

Measures

The PRO-CTCAE consists of a library of 78 symptomatic AEs assessed by 124 items. Based on a previous study among 187 pediatric clinicians from the seven pediatric hospitals listed above, 62 subjective AEs from the CTCAE were selected for their relevance for children and adolescent cancer patients. Seven of the 62 selected AEs are not included in the adult PRO-CTCAE system: dry eyes, fall, generalized muscle weakness, restlessness, suicidal ideation, sneezing, and sore throat. We developed questions to assess these seven AEs.
For each subjective AE, up to 3 questions were used to characterize the experience of the AE (Table 1).(15) The PRO-CTCAE used a 7-day reference period. The proxy version (Parent-Proxy PRO-CTCAE) had the same format and wording except we replaced the words “you” with “your child”.

In total, 131 questions from the adult PRO-CTCAE and Parent-Proxy PRO-CTCAE were evaluated in cognitive interviews among adolescents and parent-proxies, respectively. To reduce participant burden, the AEs were randomly divided among 3 forms for cognitive interviews, which included 40–44 questions per form.

**Interviewing Goals and Procedures**

The cognitive interviews were designed to determine how well participants understood the questions and could provide valid responses reflecting their own symptom experiences. Through this process (described in Figure 1), we obtained feedback on the wording of AE items, response options and reference period.

We conducted semi-structured interviews stratified by age group (13–15, 16–20 years), which represent distinct developmental stages for adolescents.(17,18) Consistent with cognitive interviewing guidelines and expert recommendations(10,19,20), our goal was to have at least 8 participants per PRO-CTCAE form and in each age group; thus, 48 interviews with adolescents and 48 interviews with proxies.

Participants first completed a paper version of the PRO-CTCAE, marking items they found hard to understand. An interviewer then asked about their responses to particular items.(20) If help or clarification was needed as participants completed the questionnaires, interviewers noted this in their field notes. Upon completion of the questionnaire and cognitive interview, each participant completed a Wide Range Achievement Test (WRAT) to assess reading level (details to be provided in another paper) and received a $25 gift card.

To standardize procedures across study sites, interviewers were trained during a one-day, in-person workshop. All interviewers and study investigators participated in weekly conference calls to discuss interview experiences, findings, and ongoing recruitment progress.

**Analytic Approach**

With consent from both the proxy and adolescent, each cognitive interview was digitally audio-recorded and recordings were subsequently transcribed. Following a cognitive interview, interviewers manually entered demographic and field note data into the Research Electronic Data Capture (REDCap) database.

Data were organized by AE term to summarize participants’ overall responses and experiences with the PRO-CTCAE items. Study team members reviewed the summarized data by age group to evaluate how well questions performed. Transcripts were reviewed to understand the source of the participant’s uncertainty. When evaluating comprehensibility, more weight was given to items when two or more adolescents had difficulties. Overall summaries were created, discussed and approved by representatives from each site to address minimum age ranges for the PRO-CTCAE and any needed modifications.
Results

Participant Characteristics

Seventy-three adolescents were approached, 22 refused, and 51 participated in cognitive interviews (24 and 27 in the 13–15 and 16–20 year-old groups, respectively) (Table 2). Forty proxy participants (21 and 19 for the 13–15 and 16–20 year-old groups, respectively) also participated.

Assessment of Symptomatic AE Terms

Of the 62 AEs evaluated, 21 AE terms had at least one 13–15 year-old who experienced difficulty with the term. Of those 21 AEs, 9 AEs had two or more 13–15 year olds who experienced difficulties. Among the 16–20 year-old group, 13 AE terms had at least one adolescent experience difficulty with the term. Of these 13 AEs, only 5 AEs had two or more 16–20 year olds experiencing difficulty. For 16–20 year olds, the majority of items were understood and few items were considered problematic to the point that further clarification was needed. Both age groups found questions about “bed sores”, “flashing lights in front of your eyes”, “anxiety”, “hot flashes”, and “bloating of the abdomen (belly)” to be difficult. Table 3 lists these items along with suggested alternative language that was understood by 7–15 year olds in our parallel work with the Pediatric PRO-CTCAE.(12) The adolescents had no trouble understanding the 7 new AE terms (see Table 4).

Assessment of the Question Structure and Response Options

In general, 13–20 year olds did not have trouble with the question structure or response options, or wording of the frequency stem. However, difficulties with the phrasing and wordiness of the severity stem were observed in both the 13–15 and 16–20 year-old participants. Seven of the 24 participants in the 13 to 15 year-old group were unable to understand the word “severity” used in the stem. The 16–20 year olds had less confusion and were able to understand the concept of severity, but suggested simpler wording. Most often, adolescents who understood the term “severity” described the concept as “how bad” the symptom was experienced. In both age groups, there was some confusion between symptom severity and interference questions (i.e., when asked to describe the meaning of severity responses) many participants discussed how often they experienced a symptom or how much it impacted their daily routine.

Assessment of the Recall Period

Most adolescents in both age groups could define a 7-day time frame. Some participants linked their reference point to their most recent treatment initiation (i.e., the reason they were in the hospital).

Overall Rating of the Survey by Adolescents

Of the 27 participants in the 16–20 year-old group, 18 described the questionnaire as “very easy” and the remaining 9 as “somewhat easy.” Of the 24 participants in the 13–15 year-old group, 19 said the questionnaire was “very easy” and 5 said it was “somewhat easy”.

J Pain Symptom Manage. Author manuscript; available in PMC 2018 April 01.
Parents/Caregivers (Proxy) Findings

Of the 40 proxy participants, 27 described the Proxy PRO-CTCAE as “very easy,” 12 as “somewhat easy,” and 1 “somewhat hard” to answer most of the questions. There were no concerns with the 7-day recall period. Overall, proxies had an easier time completing the PRO-CTCAE than their children. Of the 62 symptomatic AEs evaluated, 14 AE terms had at least one proxy experience difficulty; “flashing lights in front of your child’s eyes” and “bloating of the abdomen (belly)” were the most challenging AE items among proxies. Some proxies found the wording of the severity stem confusing and interchanged the concepts of severity with frequency and interference. Some also requested an “I don’t know” option to be added for the response options.

Discussion

As the PRO-CTCAE is becoming the standard approach to subjective AE monitoring in oncology trials for adults(6,8), there is a need to know whether the PRO-CTCAE can be validly used in younger age groups, and what adaptations might be warranted for younger ages. This study employed an innovative design to evaluate comprehension of the adult and parent-proxy versions of the PRO-CTCAE among adolescents aged 13 to 20 years and their caregivers. A diverse sample of participants from six pediatric hospitals in the United States and one site in Canada were stratified by age groups to allow us to examine questionnaire comprehension for distinct developmental stages.

Based on our cognitive interview findings, we conclude that the adult version of the PRO-CTCAE can be administered to adolescents as young as 16 years of age; whereas, the pediatric version of the PRO-CTCAE be administered to adolescents 15 years or younger. In general, we recommend the Pediatric PRO-CTCAE be used for adolescents less than 18 years. Below, we provide some recommendations for further refinements of five PRO-CTCAE AE terms and revisions of the severity question stem that proved problematic for some adolescents in our study (Table 3). Our work with the Pediatric PRO-CTCAE yielded alternative language to clarify concepts being measured.(12) Our recommendations may be considered as future refinements are made to the adult PRO-CTCAE item library; however additional cognitive interviewing and psychometric testing of our proposed alternative phrasing will need to be conducted in adults.

There were some AEs that adolescents and proxies found difficult. Some of these same items were found to be challenging in other studies. The original cognitive interview study of the PRO-CTCAE found the bed sore item to be problematic.(2) Hot flashes was the most problematic item and anxiety was challenging to understand in Spanish PRO-CTCAE cognitive testing.(21) Table 3 offers alternative language derived from our cognitive interview work conducted with younger cancer patients. We believe that if a patient has experienced these AEs, they would be able to accurately report it with the recommended wording. This alternative wording was not evaluated in 16–20 year olds, but was evaluated and determined to exhibit face validity among 7–15 year olds in our pediatric study.(12) The new AEs added to the PRO-CTCAE (Table 4) performed well and none in the 16–20 year-old group had difficulty understanding the questions and providing responses.
There were some problems with the phrasing and wordiness of the Adult PRO-CTCAE severity stem (i.e., *What was the severity of your [symptom] at its worst?*). Some adolescents had difficulty understanding the term “severity,” and others were confused by “severity” and “worst” used in the same sentence. Although our research team concluded that most participants understood what the question was asking and provided valid responses, we recommend clearer wording for this question stem. We have particular concerns for those with low literacy and for non-native English speakers. In our related work with younger cancer patients, we tested three alternative phrasings in two interview rounds. Participants consistently preferred the phrasing, “How bad was your [symptom]?” This rephrasing shortened the question length, used words that reflect the language that adolescents used in interviews, and still captured the worst severity of AE experiences.

No participants had difficulty with the Adult PRO-CTCAE questions assessing AE frequency. Adolescents and proxies had some difficulties articulating the difference between severity and interference questions; however, they were able to provide answers to probes using words that reflected their symptom experience. This represents the strong association between severity of a symptom and its impact (i.e., interference) on daily activities.

When we asked proxies for ways to improve the Proxy PRO-CTCAE, some asked to include a “don’t know” response to the response options for the questions which may reflect proxy’s uncertainty about their child’s symptom experiences. During cognitive interviews, many proxies described their child’s desire for independence and privacy; as such, proxies said they were not always aware of symptoms the way they were when their children were younger. We recommend the parent-proxy version of the PRO-CTCAE include a “don’t know” response.

When the Pediatric PRO-CTCAE is available, selection of the Pediatric versus Adult PRO-CTCAE measure for use in a clinical trial requires careful consideration, especially for adolescents given the spectrum of cognitive development observed in this population. Ideally, the same version should be used longitudinally to reduce measurement bias. For example, if a study included children 9 to 18 years of age, it may be best to use the Pediatric PRO-CTCAE for all patients. However, if a study included 15 to 30 year olds or followed older adolescents into young adulthood, then using the Adult PRO-CTCAE may be the best option. We plan to evaluate the congruency between Pediatric and Adult PRO-CTCAE instruments in a follow-up quantitative study.

Our study had several limitations. Although the sample sizes for cognitive interviews comply with guidelines(19, 20), we did not have sufficient representation in certain subgroups such as adolescents with brain/CNS tumors. This is important because the brain/CNS population could suffer from cognitive deficits likely to impact performance on these measures. Since our study was restricted to adolescents currently receiving cancer treatment, many participants were sick and fatigued, which could have limited their focus during the interviews. To reduce respondent burden and increase adolescent participation, we incorporated breaks and provided participants with a squeeze ball toy. Because interviews lasted 30–60 minutes, they required some degree of physical and emotional stamina to
complete. Consequently, our sample may be biased toward participants who are somewhat less sick than those who chose not to participate.

This study extends the scope of the adult PRO-CTCAE measure to capture symptomatic AEs in cancer populations as young as 16 years of age. In addition, this study provides a proxy version of the PRO-CTCAE to allow a different perspective of AEs to complement the adolescent’s self-report or when the adolescent can’t self-report due to illness or to cognitive conditions. Further work will evaluate the longitudinal performance of the Adult, Proxy, and Pediatric PRO-CTCAE measures in children and adolescents undergoing cancer treatment. The availability of these measures will enhance the reporting of AEs in oncology trials and may improve the quality of cancer care by directly integrating the adolescent patient’s voice.

(22)

Acknowledgments

Funding source: This work was supported by the National Cancer Institute of the National Institutes of Health [grant number R01CA175759]; and Alex’s Lemonade Stand Foundation for Childhood Cancer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or Alex’s Lemonade Stand Foundation for Childhood Cancer.

References


With permission from the treating physician, a trained study team member approaches the parent-proxy and adolescent to seek interest in participating in the study.

Interested participants (proxy and adolescent) are consented and assented by a study team member.

Interviewer asks participant open-ended questions regarding changes in their body, symptoms and emotions.

Participant completes the questionnaire and identify questions they found "Hard To Understand".

Interviewer probes participant on questions marked "Hard to Understand".

Interviewer probes participant on a select set of symptomatic adverse events.

Interviewer concludes by probing the participant on health problems that were not mentioned, difficulty of the items and ways to improve the questionnaire.

Interviewer distributes the Wide Range Achievement Test (WRAT) assessment to assess participant's reading level. Reading level was not used for eligibility.

Each participant receives a $25 incentive for participating in the cognitive interview.

Figure 1.
Flow of Semi-structured interviews with Retrospective Probing.
Table 1
PRO-CTCAE question structure and response options for each symptom AE attribute (using selected examples of symptomatic AEs).

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Question Stem</th>
<th>Response Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>In the past 7 days, how often did you have hiccups?</td>
<td>Never / Rarely / Occasionally / Frequently / Almost constantly</td>
</tr>
<tr>
<td>Severity</td>
<td>In the past 7 days, what was the severity of your itchy skin at its worst?</td>
<td>None / Mild / Moderate / Severe / Very severe</td>
</tr>
<tr>
<td>Interference</td>
<td>In the past 7 days, how much did dizziness interfere with your usual or daily activities?</td>
<td>Not at all / A little bit / Somewhat / Quite a bit / Very much</td>
</tr>
<tr>
<td>Amount</td>
<td>In the past 7 days, did you have any hair loss?</td>
<td>Not at all / A little bit / Somewhat / Quite a bit / Very much</td>
</tr>
<tr>
<td>Presence</td>
<td>In the past 7 days, did you have any increased skin sensitivity to sunlight?</td>
<td>Yes / No</td>
</tr>
</tbody>
</table>

Note: The proxy version of the PRO-CTCAE replaced the word “you” with “your child” in the question stem. [Basch et al. Development of the National Cancer Institute’s patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst. 2014;106.] For more information and permission to use PRO-CTCAE visit [http://healthcaredelivery.cancer.gov/pro-ctcae/](http://healthcaredelivery.cancer.gov/pro-ctcae/)
Table 2
Characteristics of Adolescents in Cognitive Interviews

<table>
<thead>
<tr>
<th></th>
<th>13–15 Years</th>
<th>16–20 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=24</td>
<td>%</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
<td>67</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>17</td>
<td>71</td>
</tr>
<tr>
<td>Black</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inpatient</td>
<td>9</td>
<td>38</td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>Leukemia</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>Other Solid Tumor</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Brain Tumor</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Germ Cell</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
### Table 3

Existing PRO-CTCAE symptom AE terms found challenging for some adolescents and alternative wording suggestions

<table>
<thead>
<tr>
<th>CTCAE v4.0 Term</th>
<th>Current PRO-CTCAE Wording</th>
<th>13–15 year olds with difficulty N (%)</th>
<th>16–20 year olds with difficulty N (%)</th>
<th>Key Cognitive Interview Findings</th>
<th>Suggested Candidate Phrasing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloating</td>
<td>Bloating of the abdomen (belly)</td>
<td>2 out of 8 (25%)</td>
<td>3 out of 8 (37.5%)</td>
<td>Participants did not understand the word “bloating” or thought this item was about weight gain.</td>
<td>Bigger belly than usual</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Anxiety</td>
<td>2 out of 8 (25%)</td>
<td>2 out of 8 (25%)</td>
<td>Participants did not understand the word “anxiety” or confused it with another emotion, like anger or eagerness.</td>
<td>Worried or nervous</td>
</tr>
<tr>
<td>Flashing lights</td>
<td>Flashing lights in front of your eyes</td>
<td>4 out of 8 (50%)</td>
<td>8 out of 9 (88.9%)</td>
<td>Participants associated this AE with light from an external source, such as flashlights.</td>
<td>See any flashes of light that were not there when your eyes were open or closed</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Hot flashes</td>
<td>3 out of 8 (37.5%)</td>
<td>3 out of 8 (37.5%)</td>
<td>Participants associated this AE with being outside on a hot day or being under too many blankets.</td>
<td>Feeling hot all of a sudden (hot flashes)</td>
</tr>
<tr>
<td>Skin ulceration</td>
<td>Bed sores</td>
<td>6 out of 8 (75%)</td>
<td>3 out of 8 (37.5%)</td>
<td>Participants did not understand the concept of bed sores, and discussed scenarios relating to sleeping in an uncomfortable position, or waking up with stiff muscles</td>
<td>Open sores or red spots on your skin</td>
</tr>
</tbody>
</table>

Note:

*We provide alternative wording for the AE in the sixth column based on our testing of a pediatric version of the PRO-CTCAE in children and adolescents ranging from 7 to 15 years of age. The proposed candidate phrasing should receive additional evaluation among 16–20 year olds and adult cancer patients before it is accepted into the PRO-CTCAE item library.*
Table 4
New Symptomatic AE Terms Evaluated for PRO-CTCAE in Adolescents

<table>
<thead>
<tr>
<th>CTCAE v4.0 Term</th>
<th>New PRO-CTCAE Content Evaluated in Adolescents</th>
<th>Attributes assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry eyes</td>
<td>Dry eyes</td>
<td>Frequency, severity, interference</td>
</tr>
<tr>
<td>Fall</td>
<td>Fall down</td>
<td>Frequency</td>
</tr>
<tr>
<td>Generalized Muscle Weakness</td>
<td>Arms and legs feel weak</td>
<td>Frequency, severity, interference</td>
</tr>
<tr>
<td>Restlessness</td>
<td>Not being able to sit still</td>
<td>Severity, Interference</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>Think about hurting yourself</td>
<td>Presence</td>
</tr>
<tr>
<td>Sneezing</td>
<td>Sneezing</td>
<td>Severity</td>
</tr>
<tr>
<td>Sore throat</td>
<td>Sore throat</td>
<td>Severity, Interference</td>
</tr>
</tbody>
</table>

Note: At least 8 13–15 year olds, 8 16–20 year olds, and 11 parent-proxies reviewed these items in cognitive interviews. All items were well understood. The new content should receive additional psychometric evaluation among adult cancer patients (21 years or older) before it is accepted into the PRO-CTCAE item library.