Development and Testing of the Pediatric Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (Ped-PRO-CTCAE™)

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Pediatric PRO-CTCAE™ (Ped-PRO-CTCAE™)

- Ped-PRO-CTCAE is comprised of questions that can be used to evaluate 62 symptomatic AEs drawn from the CTCAE
- Ped-PRO-CTCAE permits:
  - Self-reporting by children and adolescents ages 7-17 years (Ped-PRO-CTCAE™)
  - Caregiver-reporting by a parent or guardian when children or adolescents ages 7 to 17 years of age are unable to self-report (Ped-PRO-CTCAE™ [Caregiver])
# Pediatric Module of the Patient-Reported Outcomes version Of The Common Terminology Criteria For Adverse Events (Ped-PRO-CTCAE™)

**QUICK GUIDE TO THE ITEM LIBRARY***

<table>
<thead>
<tr>
<th>Oral</th>
<th>Respiratory</th>
<th>Visual/Perceptual</th>
<th>Mood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>Shortness of breath</td>
<td>Blurred vision</td>
<td>Anxious</td>
</tr>
<tr>
<td>Difficulty swallowing</td>
<td>Cough</td>
<td>Flashing lights</td>
<td>Sad</td>
</tr>
<tr>
<td>Mouth/throat pain</td>
<td>Wheezing</td>
<td>Watery eyes</td>
<td>Suicidal ideation</td>
</tr>
<tr>
<td>Voice quality changes</td>
<td>Sneezing</td>
<td>Ringing in ears</td>
<td></td>
</tr>
<tr>
<td>Hoarseness</td>
<td></td>
<td>Dry eyes</td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Cardio/Circulatory</th>
<th>Attention/Memory</th>
<th>Genitourinary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taste changes</td>
<td>Swelling</td>
<td>Concentration</td>
<td>Painful urination</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>Heart palpitations</td>
<td>Memory</td>
<td>Urinary urgency</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urinary frequency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cutaneous</th>
<th>Pain</th>
<th>Sleep/Wake</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin dryness</td>
<td>General pain</td>
<td>Insomnia</td>
<td>Bruising</td>
</tr>
<tr>
<td>Acne</td>
<td>Headache</td>
<td>Fatigue</td>
<td>Chills</td>
</tr>
<tr>
<td>Hair loss</td>
<td>Muscle pain</td>
<td></td>
<td>Increased sweating</td>
</tr>
<tr>
<td>Itching</td>
<td>Joint pain</td>
<td></td>
<td>Hot flashes</td>
</tr>
<tr>
<td>Hives</td>
<td></td>
<td></td>
<td>Nosebleed</td>
</tr>
<tr>
<td>Sensitivity to sunlight</td>
<td></td>
<td></td>
<td>Falls</td>
</tr>
<tr>
<td>Skin ulceration</td>
<td></td>
<td></td>
<td>Muscle weakness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurological</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbness &amp; tingling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Attributes**

<table>
<thead>
<tr>
<th>F: Frequency</th>
<th>I: Interference</th>
<th>S: Severity</th>
<th>P: Presence/Absence</th>
</tr>
</thead>
</table>

*Complete library of items available at: https://healthcaredelivery.cancer.gov/pro-ctcae

NIH National Cancer Institute

2/7/2021
## Ped-PRO-CTCAE™: Attributes and Item Structures

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Severity</th>
<th>Interference</th>
<th>Presence/Absence</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often did you have ______?</td>
<td>How bad was your ______?</td>
<td>How much did _____ keep you from doing things you usually do?</td>
<td>Did you have ______?</td>
</tr>
<tr>
<td>• Never</td>
<td>• Did not have any</td>
<td>• Not at all</td>
<td>• No</td>
</tr>
<tr>
<td>• Sometimes</td>
<td>• A little bad</td>
<td>• Some</td>
<td>• Yes</td>
</tr>
<tr>
<td>• Most of the time</td>
<td>• Bad</td>
<td>• A lot</td>
<td>• I do not know</td>
</tr>
<tr>
<td>• Almost all the time</td>
<td>• Very bad</td>
<td>• A whole lot</td>
<td></td>
</tr>
</tbody>
</table>

- Recall period is the past 7 days
- Each symptomatic AE is assessed by 1-3 attributes
- Conditional branching logic within PRO-CTCAE items can be implemented when using electronic data capture, thereby reducing respondent burden
- Ped-PRO-CTCAE [Caregiver] employs comparable attributes; phrasing of items for caregiver-reporting replaces “you” with “your child”

For more information visit: [http://healthcaredelivery.cancer.gov/pro-ctcae/](http://healthcaredelivery.cancer.gov/pro-ctcae/)
### CTCAE vs. Ped-PRO-CTCAE™ Item Structures

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CTCAE Term:</strong> Pain</td>
<td>No pain</td>
<td>Mild pain</td>
<td>Moderate pain; limiting instrumental ADL</td>
<td>Severe pain; limiting self care ADL</td>
</tr>
</tbody>
</table>

1) In the past 7 days, how often did you have **pain**?
   - Never
   - Sometimes
   - Most of the time
   - Almost all the time

2) In the past 7 days, how bad was your **pain**?
   - Did not have any
   - A little bad
   - Bad
   - Very bad

3) In the past 7 days, how much did **pain** keep you from doing things you usually do?
   - Not at all
   - Some
   - A lot
   - A whole lot
Ped-PRO-CTCAE™
Development and Testing
Ped-PRO-CTCAE™: Concept Elicitation±

Objective:
- Identify CTCAE terms that are both important to evaluate in pediatric oncology trials and amenable to child self-report

Methods:
- 187 experienced pediatric oncology clinicians reviewed 790 CTCAE terms

Results:
- 64* symptomatic AE terms determined to be highly salient for children and adolescents ages 7-17 years undergoing cancer treatment were identified through 2 rounds of surveys

* Note: Symptom terms “fever” and “vaginal discharge” did not advance for item development

± This work was partially funded by a grant from the Alex’s Lemonade Stand Foundation for Childhood Cancer

Ped-PRO-CTCAE™: Item Development

Objective:
- Develop a library of items that capture symptomatic AEs by self-report in children ages 7-17, and by caregiver-report in children younger than 7

Methods:
- Trialists, clinical experts, PRO methodologists, and patient advocates employed best practices for the design of pediatric patient-reported outcomes measures

Results:
- 130 items developed to evaluate 62 symptom terms
  - Each symptomatic AE is assessed with 1-3 attributes
  - 7-day recall period
  - Items for caregiver-reporting on behalf of children younger than 7 years of age employ comparable attributes; phrasing replaces “you” with “your child”
Ped-PRO-CTCAE™: Content Validity

Objective:
- Conduct cognitive interviews with children and their caregivers to assess comprehension, clarity and ease of judgement of the Ped-PRO-CTCAE and Ped-PRO-CTCAE [Caregiver]

Methods:
- 2 rounds of cognitive interviews with children (n=81) and caregiver-proxies (n=74)
  - Is the phrasing of the Ped-PRO-CTCAE questions and response choices well comprehended and clear?
  - Do children of different ages interpret symptom terms in the same way?
  - Do children understand and provide valid answers to PRO-CTCAE questions?
  - How does the recall period affect responses?

Ped-PRO-CTCAE™: Content Validity

Results:

- Most participants rated items as “very easy” or “somewhat easy” to understand, and were able to read, understand, and provide valid responses to the questions.
- Minor refinements were made to the items between interview rounds 1 and 2 to improve comprehension and clarity; retested with good comprehension.
- All Ped-PRO-CTCAE and Ped-PRO-CTCAE [Caregiver] items were well-comprehended by a majority of children/adolescents ages 7 to 17 and their caregivers in a second round of interviews.
- Some symptomatic AEs reflecting rare events (e.g. wheezing, hot flashes) were challenging to comprehend.

Objective:
- Evaluate construct validity, responsiveness, and test-retest reliability of Ped-PRO-CTCAE items among children and adolescents undergoing cancer treatment at one of 9 pediatric oncology hospitals

Methods:
- **Sample size:** 482 triads – child, caregiver, clinician
  - N = 203: 7-12 years old
  - N = 144: 13-15 years old
  - N = 135: 16-18 years old
- **Inclusion criteria for child participants:**
  - First cancer diagnosis (any cancer type)
  - Completed at least one month of frontline treatment
  - Currently receiving cancer-directed therapy
Ped-PRO-CTCAE™: Validity and Reliability

**Baseline (T1)**
72 hours preceding treatment initiation

**Follow-up (T2)**
Approximately 7–17 days later for chemotherapy, and 4+ weeks later for radiation

*Note: Test-retest reliability was conducted in an independent sample of 46 children receiving acute lymphoblastic leukemia (ALL) treatment in the maintenance phase of therapy (weeks 50-126+). Assessments for test-retest were obtained 5-9 days apart.*
Ped-PRO-CTCAE™: Validity and Reliability

- Ped-PRO-CTCAE items demonstrated strong convergent and known-groups validity, test-retest reliability, and responsiveness over time
  - Observations were consistent across age groups and at each time point
- **Convergent validity**: Ped-PRO-CTCAE correlated with other conceptually relevant patient-reported outcome measures
  - Strong correlations among symptoms measured by Ped-PRO-CTCAE and MSAS across different ages at T2, $r=0.62-0.98$
  - Strong correlations between individual Ped-PRO-CTCAE symptomatic AEs and PROMIS Pediatric domains at T2, $r=0.63-0.76$
- **Known-groups validity**:
  - Ped-PRO-CTCAE items meaningfully differentiated children by Lansky Play-Performance Status and medication use
  - Convergent & discriminant validity, known grouped validity, responsiveness & stability of Ped-PRO-CTCAE [Caregiver] demonstrated in a sample of caregivers of children & adolescents ages 7-17

Ped-PRO-CTCAE™: Validity and Reliability

Results:

- **Test-retest reliability:**
  - Agreement between Ped-PRO-CTCAE reports captured on two occasions approximately 7 days apart ranged from 54% to 93%

- **Responsiveness:**
  - Moderate to strong associations between change in Ped-PRO-CTCAE and MSAS over time

- **Ped-PRO-CTCAE [Caregiver]**
  - Convergent and discriminant validity, known groups validity, responsiveness and stability of Ped-PRO-CTCAE [Caregiver] demonstrated in a sample of caregivers of children and adolescents ages 7-17 years

Ped-PRO-CTCAE™: Scoring and Interpretation
Ped-PRO-CTCAE™: Interpretation and Reporting

- Each symptomatic AE is assessed by 1-3 items representing different symptom attributes (frequency, severity, interference or presence/absence)
- Most questions have 4-point ordinal response scale and are scored from 0-3
- Each individual item is scored separately yielding up to three scores per symptomatic toxicity
  - Ped-PRO-CTCAE Score ≠ Clinician CTCAE Grade
  - Best way to combine the attributes (frequency, severity, interference) and to interpret the scores has not been established and is under study
  - Descriptive reporting of available attributes is recommended
  - Significant additional scientific study is needed before individual-level PRO-CTCAE scores can be used for clinical and protocol-specific decision-making (e.g. dose adjustments)
Ped-PRO-CTCAE™: Reporting

- Ped-PRO-CTCAE data should be presented descriptively for each symptomatic AE
- Example: Child reports over the past 7 days:
  - Pain Frequency: “Most of time”
  - Pain Severity: “Bad”
  - Pain Interference with daily activities: “A lot”
Conclusions

- Measurement properties of Ped-PRO-CTCAE have been rigorously evaluated using qualitative and quantitative methods
  - Evidence supports its use to capture symptomatic toxicity using child self-report or caregiver-report in pediatric oncology trials
  - Ped-PRO-CTCAE has been incorporated into several planned and ongoing Phase I, II, and III pediatric oncology studies
- Pediatric PRO-CTCAE module is currently available in English, Italian and Simplified Chinese
- Additional languages currently being tested include Spanish, German, Korean, Danish, French (for Canada), French (for Europe).
  - For more information visit: http://healthcaredelivery.cancer.gov/pro-ctcae/
- Ongoing analyses:
  - Comparison of the measurement properties of Ped-PRO-CTCAE and PRO-CTCAE in respondents ages 16-18 to determine the lowest age at which PRO-CTCAE is comprehended
  - Evaluation of concordance among reports provided by child, caregiver, and clinician
Ped-PRO-CTCAE™ Development Team

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  - Mia Waldron
- Cornell University
  - Laura Pinheiro
- Dana Farber Cancer Institute
  - Jenny Mack
- Duke University
  - Bryce Reeve
  - Molly McFatrich
  - Nicole Lucas
  - Li Lin
- Emory University / Children’s Healthcare of Atlanta
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  - Sharon Castellino
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  - Judy Bosi
- Hospital for Sick Children
  - Lillian Sung
  - Deborah Tomlinson
- University of North Carolina
  - Ethan Basch
  - Antonia Bennett
  - Stuart Gold

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For more information about the PRO-CTCAE™ Measurement System visit: https://healthcaredelivery.cancer.gov/pro-ctcae