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

Bryce B. Reeve, PhD
Professor, Population Health Sciences
Professor, Pediatrics
Director, Center for Health Measurement
Duke University School of Medicine

Pamela S. Hinds, PhD, RN, FAAN
The William and Joanne Conway Chair in Nursing Research
Executive Director, Department of Nursing Science,
Professional Practice, and Quality Outcomes
Children's National Hospital

Developed with Funding From the National Cancer Institute: R01CA175759 (PIs: Hinds and Reeve)

NIH NATIONAL CANCER INSTITUTE
Division of Cancer Control & Population Sciences

April 15, 2021

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*

Oral	
Dry mouth	SI
Difficulty swallowing	S
Mouth/throat pain	FSI
Voice quality changes	PI
Hoarseness	FSI
Sore throat	SI

Gastrointestinal	
Taste changes	PI
Decreased appetite	F
Nausea	FSI
Vomiting	FI
Heartburn	FS
Gas	PI
Bloating	PI
Hiccups	FS
Constipation	FSI
Diarrhea	FI
Abdominal pain	FSI
Fecal incontinence	FI

Respiratory	
Shortness of breath	FSI
Cough	FSI
Wheezing	SI
Sneezing	S

Cardio/Circulatory	
Swelling	SI
Heart palpitations	FS

Cutaneous	
Skin dryness	P
Acne	S
Hair loss	P
Itching	SI
Hives	P
Sensitivity to sunlight	P
Skin ulceration	P

Neurological	
Numbness & tingling	SI
Dizziness	SI

Visual/Perceptual	
Blurred vision	PI
Flashing lights	FI
Watery eyes	FSI
Ringing in ears	SI
Dry eyes	FSI

Attention/Memory	
Concentration	SI
Memory	SI

Pain	
General pain	FSI
Headache	FSI
Muscle pain	FSI
Joint pain	FSI

Sleep/Wake	
Insomnia	FSI
Fatigue	SI

Mood	
Anxious	FSI
Sad	SI
Suicidal ideation	P

Genitourinary	
Painful urination	SI
Urinary urgency	FI
Urinary frequency	FI
Change in usual urine color	P
Urinary incontinence	FI

Miscellaneous	
Bruising	P
Chills	FS
Increased sweating	FSI
Hot flashes	FSI
Nosebleed	FSI
Falls	F
Muscle weakness	FSI
Restlessness	SI

Attributes	
F: Frequency	I: Interference
S: Severity	P: Presence/Absence

NIH National Cancer Institute

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

2/7/2021

Ped-PRO-CTCAE™: Attributes and Item Structures

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

- 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/

CTCAE vs. Ped-PRO-CTCAE™ Item Structures

Adverse Event	Grade 0	Grade 1	Grade 2	Grade 3
CTCAE Term: Pain	No pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL

Ped-PRO-CTCAE™

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

Reeve et al. (2013). *Pediatric Blood & Cancer.*, 60(7):1231-6. doi: 10.1002/pbc.24463

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?

Reeve et al. (2017). *Pediatr Blood Cancer.*, 64(3). doi: 10.1002/pbc.26261
Reeve et al. (2017). *J Pain Symtom Managment.*, 53(4):759-766. doi: 10.1016/j.jpainsymman.2016.11.006

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

Reeve et al. (2017). *Pediatr Blood Cancer.*, 64(3). doi: 10.1002/pbc.26261
Reeve et al. (2017). *J Pain Symtom Managment.*, 53(4):759-766. doi: 10.1016/j.jpainsymman.2016.11.006

Ped-PRO-CTCAE™: Validity and Reliability

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

Treatment

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

Reeve et al.(2020). *Cancer*, 30. doi: 10.1002/cncr.33389
Reeve et al.(2020). JNCI., 30. doi: 10.1093/jnci/djaa016

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

Reeve et al.(2020). *Cancer*, 30. doi: 10.1002/cncr.33389
Reeve et al.(2020). JNCI., 30. doi: 10.1093/jnci/djaa016

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

- **Children's Hospital of Los Angeles**
  - David Freyer
  - Katie Villabroza
- **Children's Hospital of Pittsburgh**
  - Scott Maurer
  - Sharon DiBridge
  - Mary Petrany
- **Children's National Health System**
  - Pamela Hinds
  - Shana Jacobs
  - Catriona Mowbray
  - 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**
  - Janice Withycombe
  - Sharon Castellino
- **St. Jude Children's Research Hospital**
  - Justin Baker
  - Judy Bosi
- **Hospital for Sick Children**
  - Lillian Sung
  - Deborah Tomlinson
- **University of North Carolina**
  - Ethan Basch
  - Antonia Bennett
  - Stuart Gold

We are very grateful to the participants in our studies for their help in designing these measures for children and their families

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