National Cancer Institute’s Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) Measurement System: An Overview

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Overview and Background
Measuring Safety and Tolerability in Cancer Clinical Trials

Safety and tolerability are fundamental to conclusions about the effectiveness of cancer therapies, including comparative effectiveness. In cancer clinical trials, adverse events are graded and reported using Common Terminology Criteria for Adverse Events (CTCAE) (now in version 5). Validity of symptom reports may be eroded when filtered through research staff and clinicians.

10% of the 800 adverse events listed in CTCAE are symptoms and thus are amenable to self-reporting. Staff-based AE reporting occurs at clinic visits; AEs occurring between visits may be missed.

Capturing Symptomatic Adverse Events Using Patient-Reported Outcomes

- Real-time ascertainment of symptomatic adverse events using PROs can improve the precision and reproducibility of adverse event reporting.

- NCI’s Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) Measurement System
  - PRO measurement system developed to allow patient self-reporting of the presence/absence, frequency, severity and/or interference of symptomatic adverse events
  - Designed to be used as a companion to the CTCAE to capture the patient experience of symptomatic toxicities in cancer clinical trials

PRO-CTCAE™ Measurement System

- Symptomatic adverse events amenable to self-reporting were identified from CTCAE
- PRO-CTCAE items evaluate the symptom attributes of frequency, severity, interference, amount, presence/absence
- Conditional branching logic can be implemented with electronic data capture, thereby reducing respondent burden
- PRO-CTCAE linguistically validated in more than 40 languages
- Pediatric module permits self-reporting by children and adolescents ages 7-17 years (Ped-PRO-CTCAE™) or caregiver-reporting for children ages 7-17 who are unable to self-report (Ped-PRO-CTCAE™ [Caregiver])

For more information visit: [https://healthcaredelivery.cancer.gov/pro-ctcae](https://healthcaredelivery.cancer.gov/pro-ctcae)
PRO-CTCAE™ Attributes and Item Structures

- 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
CTCAE vs. PRO-CTCAE™ Item Structures

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Mucositis oral</td>
<td>Asymptomatic or mild symptoms; intervention not indicated</td>
</tr>
</tbody>
</table>

PRO-CTCAE

Please think back over the past 7 days:

What was the severity of your MOUTH OR THROAT SORES at their WORST?
None / Mild / Moderate / Severe / Very severe

How much did MOUTH OR THROAT SORES interfere with your usual or daily activities?
Not at all / A little bit / Somewhat / Quite a bit / Very much

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])
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></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/)
PRO-CTCAE™ Measurement System

- Psychometrically robust library of items
- Accommodate diverse linguistic preferences
- Permit self-reporting by respondents across the developmental spectrum
- Supply meaningful data to improve understanding of symptomatic AEs
### PRO-CTCAE™: Content Validity

**Objective:**
- Develop the items and examine the content validity of the PRO-CTCAE item library

**Methods:**
- Trialists, clinical experts, PRO methodologists, patient advocates, and representatives from the US Food and Drug Administration identified symptomatic AEs that can be meaningfully self-reported by patients
- Three rounds of semi-structured cognitive interviews were conducted to evaluate comprehension, clarity and ease of judgement (N=127)
- PRO-CTCAE items were iteratively refined between interview rounds

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**Results:**
- 78 symptomatic AEs identified from the more than 800 terms in the CTCAE lexicon; plain-language symptomatic AE terminologies developed
- Each symptomatic AE term is assessed using 1 to 3 items
- Frequency, severity, interference w/ daily activities, presence/absence, amount
- Cognitive interviewing using structured and open-ended probes (N=127)
  - 63/80 symptom terms generated no cognitive difficulties; 17 modified and re-tested without further comprehension difficulties

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1. Basch et al. (2014). *JNCI.*, 106(9). pii: dju244. doi: 10.1093/jnci/dju244
PRO-CTCAE™: Validity and Reliability

Objective:

- Evaluate the quantitative measurement properties of PRO-CTCAE, specifically validity, reliability, sensitivity, and mode equivalence.

Methods:

- 975 patients who had received cancer-directed therapy in the prior two weeks were recruited and completed PRO-CTCAE surveys and EORTC QLQ C30
  - Convergent validity: associations with EORTC QLQ C30 scores
  - Known-groups validity based on disease site, clinical characteristics, and ECOG PS
  - Test-retest reliability: assessed on consecutive days in a subsample

Sample was diverse with respect to age, disease site, and performance status:

- 59 years (range 19-91); 82% White; 32% < high school; 35% lung/head and neck; 28% breast; 18% GU/Gyn; 17% PS 2-4

Results:

- PRO-CTCAE exhibits favorable validity, reliability, and responsiveness.
- Most PRO-CTCAE items (118/124) reached a statistically significant ($p<.05$) and meaningful effect size on one or more a priori validity criteria
- 6 items (rare events with low endorsement) could not be meaningfully validated in this sample
- All PRO-CTCAE items were associated with conceptually-relevant EORTC QLQ-C30 domains
- 96/124 PRO-CTCAE items distinguished subgroups based on performance status, disease site, and/or treatment characteristics

PRO-CTCAE™: Validity and Reliability

**Results:**

- Acceptable test-retest reliability exhibited across subset of items tested (Median ICC 0.77)
- Response choices are well comprehended; each of the ordinal response choices is nonoverlapping and distinguishes respondents with meaningfully different symptom experiences


PRO-CTCAE™: Mode Equivalence

- N=112 patients completed 28 PRO-CTCAE items (14 symptomatic A/Es) by each of the three modes of administration at a single clinic visit
- Average time to complete an item:
  - Web: 11.1 seconds (SD = ±8.4)
  - Interactive Voice Response (IVRS): 16.3 seconds (SD = ±6.3)
  - Paper: 10.3 seconds (SD = ±5.8)

<table>
<thead>
<tr>
<th></th>
<th>Median ICC (Range)</th>
<th>Median (range) between-mode item-level mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Web vs IVRS</td>
<td>0.78 (0.56 - 0.90)</td>
<td>-0.04 (-0.16 - 0.22)</td>
</tr>
<tr>
<td>Web vs paper</td>
<td>0.81 (0.61 - 0.96)</td>
<td>-0.02 (-0.11 - 0.14)</td>
</tr>
<tr>
<td>IVRS vs paper</td>
<td>0.78 (0.59 - 0.91)</td>
<td>0.02 (-0.07 - 0.19)</td>
</tr>
</tbody>
</table>

Between modes, item-level mean differences were very small, and the corresponding effect sizes were all less than 0.20

N=110 patients completed 27 PRO-CTCAE™ items (14 symptomatic A/Es)

- Comparison of 28 daily ratings to 1-, 2-, 3-, and 4-week recalled ratings
- Mean difference between the average daily score and recalled score

1-week recall corresponds well to daily reporting. Differences between daily and longer recall periods widen with 2-, 3-, and 4-week recall


PRO-CTCAE™: Comparison of Recall Periods

**PRO-CTCAE™ Development Team**

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Paul Kluetz

Reshma Koganti

Virginia Kwitkowski

Pauline La

Suzanne Lechner

Lauren Lent

Yuelin Li

Carol Lowenstein

Donna Malveaux

Mauricio Medina

Michael Mejia

Tito Mendoza

Michael Montello

Cuong Nguyen

Hannah O’Gorman

Ann O’Mara

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We gratefully acknowledge our study participants and patient representatives!
PRO-CTCAE™ in Cancer Clinical Trials: Study Design, Analysis and Interpretation

Study Design Considerations

- PRO-CTCAE is designed to be used in conjunction with CTCAE
  - Provides complimentary information
  - Timing of assessments should be comparable and data reported in parallel
- Item selection and timing of assessment are critical design decisions to reduce risk of bias and maximize interpretability and utility of results
- Study design and analysis plan should consider published guidelines for protocol development and statistical analysis of studies that include a patient-reported outcome\(^1,2\)

Study Design Considerations

- Which toxicities to be measured?
  - Based on CTCAE-graded toxicities observed in earlier phase studies of agent, knowledge of drug class, and anticipated on- and off-target effects; qualitative work in the population (if it exists); input from investigators
  - Consistent with CAEPR as presented in the study protocol
  - Same PRO-CTCAE items in both study arms
  - Thoughtful item selection to minimize patient burden

- At what time points of measurement?
  - Baseline, regular intervals during treatment, at treatment discontinuation
  - Toxicity surveillance using CTCAE and PRO-CTCAE™ elements should reflect comparable timeframes

- Planned analysis (descriptive and graphical)
- Inclusion of back-up data collection strategies and real-time monitoring of data quality to limit missing data
- Free-text write-ins for unsolicited symptoms
Interpretation and Reporting

- PRO-CTCAE Score ≠ Clinician CTCAE Grade
- Up to three patient-reported scores per symptomatic toxicity
- Best way to combine the attributes (frequency, severity, interference) and to interpret the scores has not been established and is under study
- CTCAE Grade 4 does not exist for most of the PRO-CTCAE toxicities
- Descriptive reporting of available attributes is recommended
- Significant additional scientific study focused on validity and interpretability is needed before individual-level PRO-CTCAE scores can be used for clinical and protocol-specific decision-making (e.g. dose adjustments)
- PRO-CTCAE data is not included in FDA clinical site inspections or IND safety reporting, but descriptive findings, and missing data/data quality should be available for review by the DSMB

Expanding Adoption and Implementation

- Collaborations with leading national and international organizations to enhance uptake and adoption in clinical trials
  - NCI National Clinical Trials Network (NCTN) and Early Therapeutics Clinical Trials Network (ETCTN)
  - Regulatory: US Food and Drug Administration, NHS in UK, EMA
  - International: Italian NCI, Japanese NCI, Danish Cancer Society, German Society of Hematology and Medical Oncology (DGHO)
- PRO-CTCAE has been linguistically validated in more than 40 languages; 20 additional languages currently in development and validation
- Pediatric module available in English, Italian and Chinese; additional validation studies ongoing

Strengthening Interpretability and Clinical Utility

- Interpretation and clinical utility of PRO-CTCAE still evolving
  - Continued implementation in early phase trials, precision medicine studies and randomized trials
  - Anticipate future novel trial designs incorporating PRO-CTCAE data in real time for dose-finding and tailoring therapy for vulnerable subgroups
- Ongoing work to enhance interpretability and utility of PRO-CTCAE
  - Empirically-derived mapping of PRO-CTCAE item scores into CTCAE grades using a discrete choice methodology to establish IRT metric
  - Adopters in surgical oncology, immuno-oncology, and radiation oncology testing items to expand the item library
  - Additional languages undergoing linguistic validation through a series of CRADAs
  - Evaluate different approaches to patient-investigator grade reconciliation and to analyzing and representing PRO-CTCAE data and strengthening the analysis and interpretation of PRO-CTCAE and CTCAE data jointly, thereby improving our understanding of treatment tolerability
Improving our Understanding of the Tolerability of Cancer Treatments

- PRO reporting of symptomatic adverse events is
  - Crucial to patients, their clinicians, trial sponsors, and regulators
  - Essential to determinations of benefit and harm at the study level
- PRO-CTCAE will ultimately be interpreted within the CTCAE reporting framework
- Ongoing efforts to embed PRO-CTCAE into cancer treatment trials and observational studies will provide
  - Understanding of how reporting could influence dose modifications
  - Evidence-based principles for PRO-CTCAE-related study design and trial workflow
  - Understanding of treatment tolerability as an endpoint that is interpretable and useful for decision-making at both the individual and trial-level

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