# 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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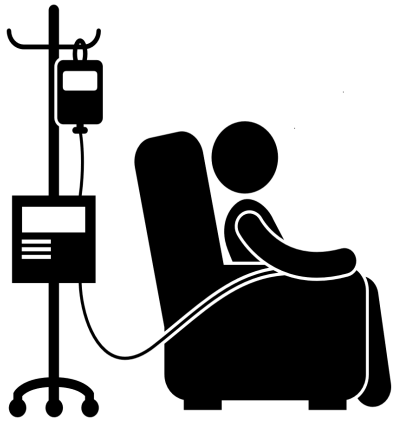
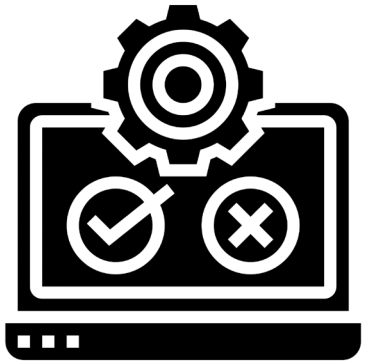
# Overview and Background

# Measuring Safety and Tolerability in Cancer Clinical Trials

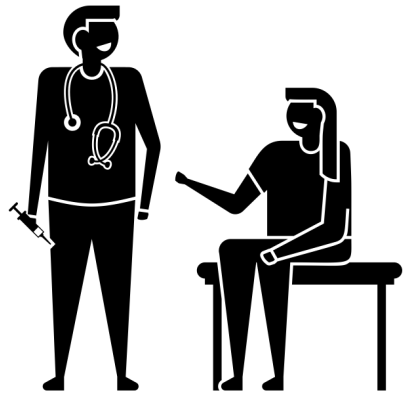


Safety and tolerability are fundamental to conclusions about the effectiveness of cancer therapies, including comparative effectiveness



In cancer clinical trials, adverse events are graded and reported using Common Terminology Criteria for Adverse Events (*CTCAE*) (now in version 5)

10% of the 800 adverse events listed in CTCAE are symptoms and thus are amenable to self-reporting



Validity of symptom reports may be eroded when filtered through research staff and clinicians[1]

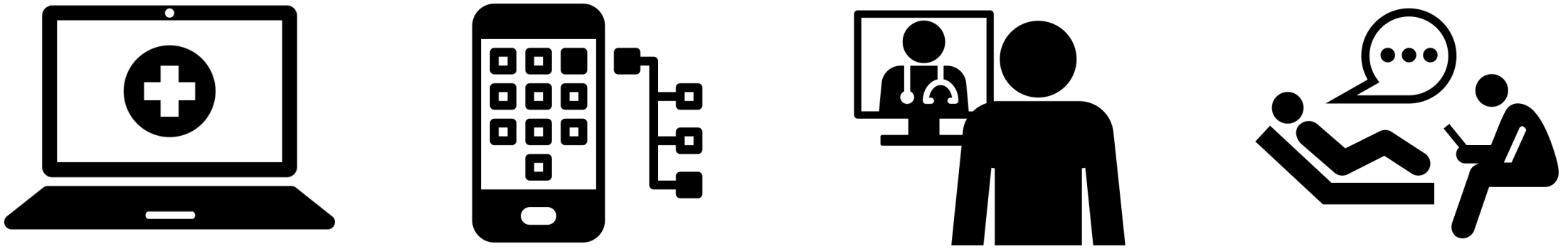
Staff-based AE reporting occurs at clinic visits; AEs occurring between visits may be missed



[1]Xiao et al. (2013). *Cancer Nurs.*,36(6):E1-E16. doi: 10.1097/NCC.0b013e318269040f

# 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



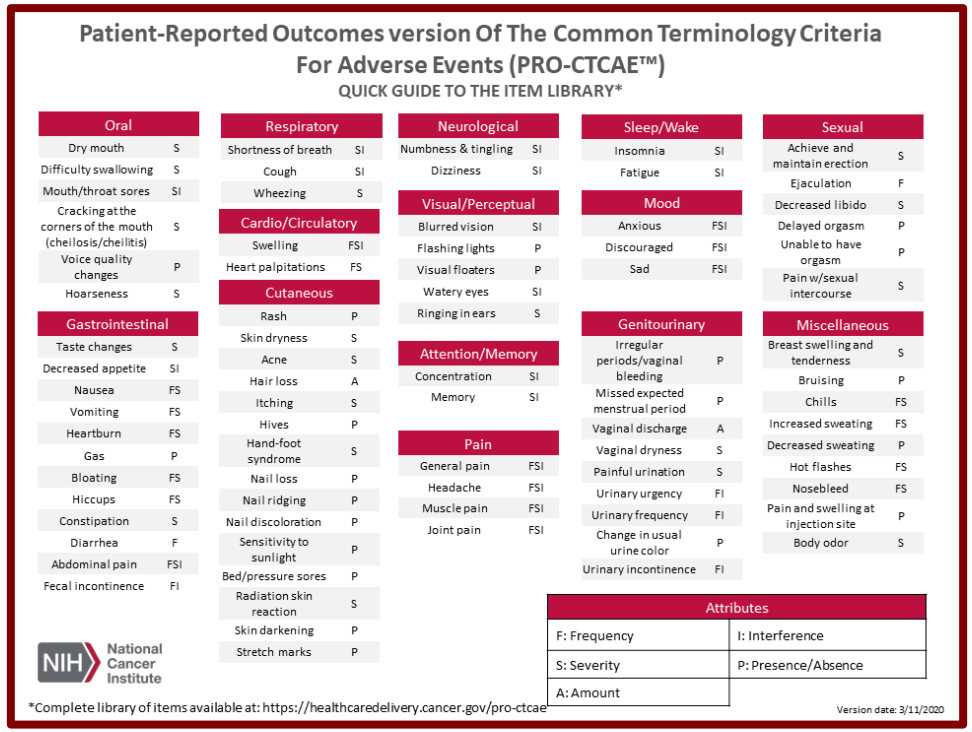
- **NCI's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) Measurement System**
  - PRO measurement system developed to allow patient self-reporting of the presence/absence, frequency, severity and/or interference of symptomatic adverse events
  - Designed 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 25 languages
- Pediatric module permits self-reporting by children and adolescents ages 7-17 years (Ped-PRO-CTCAE™) or caregiver-reporting for children younger than 7 years of age (Ped-PRO-CTCAE™ [Caregiver])

# PRO-CTCAE™ Measurement System

- Investigators select for prospective surveillance those PRO-CTCAE items that reflect anticipated symptomatic toxicities
- Custom surveys in more than 25 languages can be created using the Form Builder function at the NCI PRO-CTCAE website



**Patient-Reported Outcomes version Of The Common Terminology Criteria For Adverse Events (PRO-CTCAE™)**

QUICK GUIDE TO THE ITEM LIBRARY*

| Oral | |
|---|---|
| Dry mouth | S |
| Difficulty swallowing | S |
| Mouth/throat sores | SI |
| Cracking at the corners of the mouth (cheilosis/cheilitis) | S |
| Voice quality changes | P |
| Hoarseness | S |

| Gastrointestinal | |
|---|---|
| Taste changes | S |
| Decreased appetite | SI |
| Nausea | FS |
| Vomiting | FS |
| Heartburn | FS |
| Gas | P |
| Bloating | FS |
| Hiccups | FS |
| Constipation | S |
| Diarrhea | F |
| Abdominal pain | FSI |
| Fecal incontinence | FI |

| Respiratory | |
|---|---|
| Shortness of breath | SI |
| Cough | SI |
| Wheezing | S |

| Cardio/Circulatory | |
|---|---|
| Swelling | FSI |
| Heart palpitations | FS |

| Cutaneous | |
|---|---|
| Rash | P |
| Skin dryness | S |
| Acne | S |
| Hair loss | A |
| Itching | S |
| Hives | P |
| Hand-foot syndrome | S |
| Nail loss | P |
| Nail ridging | P |
| Nail discoloration | P |
| Sensitivity to sunlight | P |
| Bed/pressure sores | P |
| Radiation skin reaction | S |
| Skin darkening | P |
| Stretch marks | P |

| Neurological | |
|---|---|
| Numbness & tingling | SI |
| Dizziness | SI |

| Visual/Perceptual | |
|---|---|
| Blurred vision | SI |
| Flashing lights | P |
| Visual floaters | P |
| Watery eyes | SI |
| Ringing in ears | S |

| Attention/Memory | |
|---|---|
| Concentration | SI |
| Memory | SI |

| Pain | |
|---|---|
| General pain | FSI |
| Headache | FSI |
| Muscle pain | FSI |
| Joint pain | FSI |

| Sleep/Wake | |
|---|---|
| Insomnia | SI |
| Fatigue | SI |

| Mood | |
|---|---|
| Anxious | FSI |
| Discouraged | FSI |
| Sad | FSI |

| Genitourinary | |
|---|---|
| Irregular periods/vaginal bleeding | P |
| Missed expected menstrual period | P |
| Vaginal discharge | A |
| Vaginal dryness | S |
| Painful urination | S |
| Urinary urgency | FI |
| Urinary frequency | FI |
| Change in usual urine color | P |
| Urinary incontinence | FI |

| Sexual | |
|---|---|
| Achieve and maintain erection | S |
| Ejaculation | F |
| Decreased libido | S |
| Delayed orgasm | P |
| Unable to have orgasm | P |
| Pain w/sexual intercourse | S |

| Miscellaneous | |
|---|---|
| Breast swelling and tenderness | S |
| Bruising | P |
| Chills | FS |
| Increased sweating | FS |
| Decreased sweating | P |
| Hot flashes | FS |
| Nosebleed | FS |
| Pain and swelling at injection site | P |
| Body odor | S |

| Attributes | |
|---|---|
| F: Frequency | I: Interference |
| S: Severity | P: Presence/Absence |
| A: Amount | |

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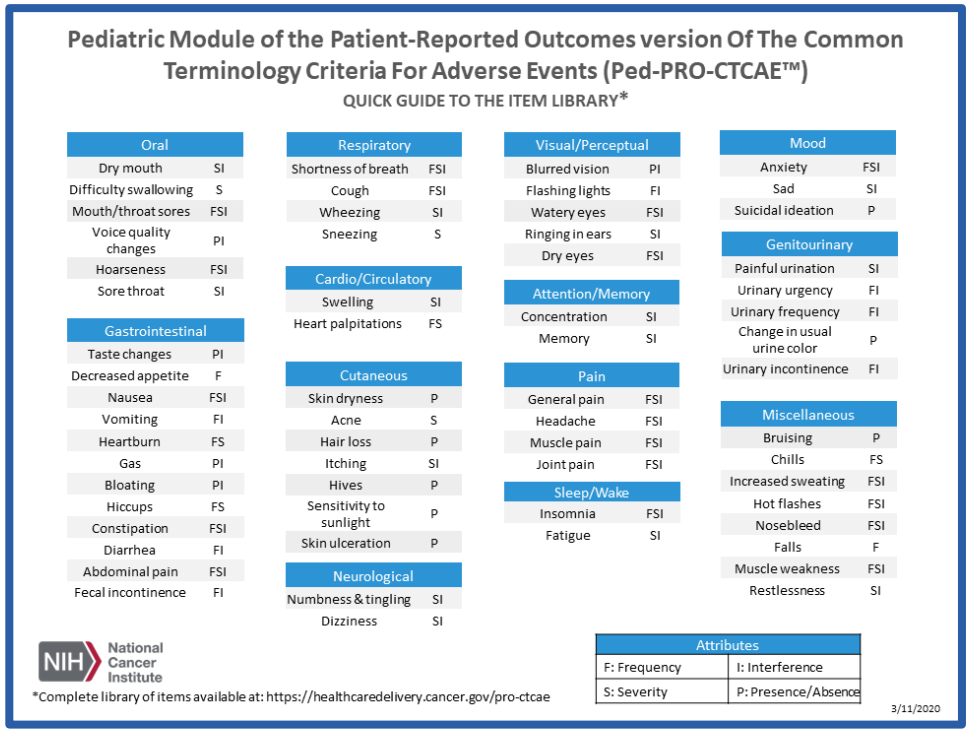
*Complete library of items available at: https://healthcaredelivery.cancer.gov/pro-ctcae

Version date: 3/11/2020



**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 sores | 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 | |
|---|---|
| Anxiety | 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 |

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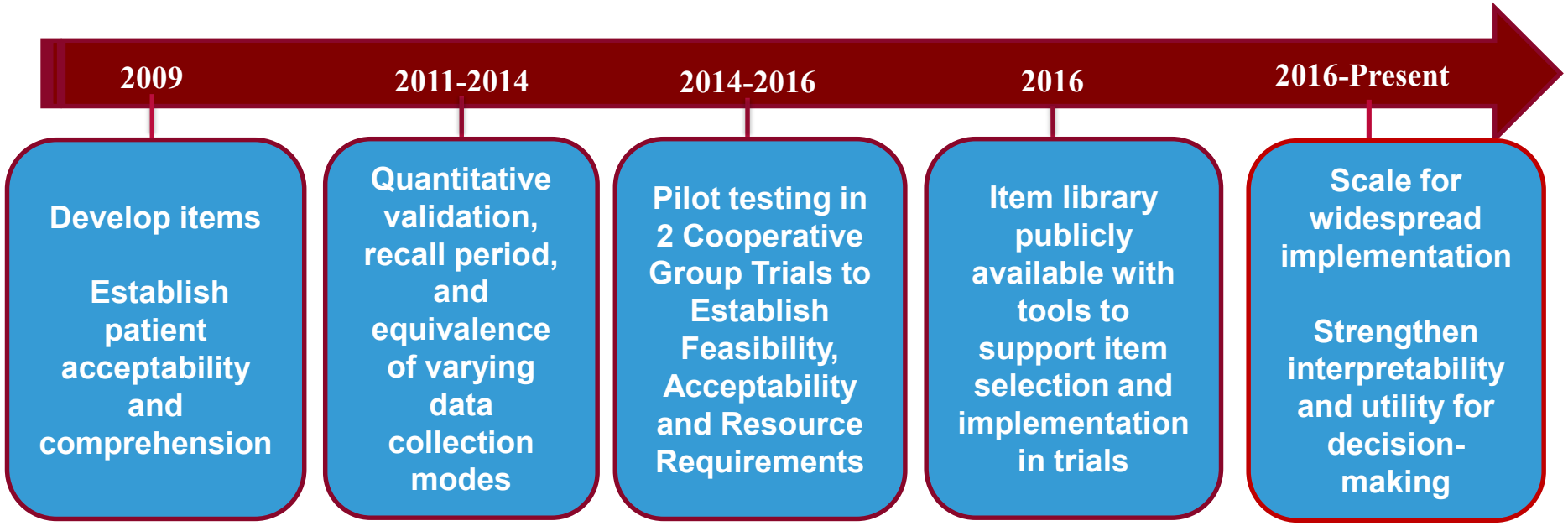
*Complete library of items available at: https://healthcaredelivery.cancer.gov/pro-ctcae

3/11/2020

# PRO-CTCAE™ Measurement System

- Psychometrically robust library of items
- Accommodate respondents who speak languages other than English
- Permit self-reporting by respondents across the developmental spectrum
- Supply meaningful data to improve understanding of symptomatic AEs



# PRO-CTCAE™
# Development and Measurement Properties

# 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[1]
- Three rounds of semi-structured cognitive interviews were conducted to evaluate comprehension, clarity and ease of judgement (N=127)[2]
- PRO-CTCAE items were iteratively refined between interview rounds

[1]Basch et al. (2014). *JNCI.*, 106(9). pii: dju244. doi: 10.1093/jnci/dju244

[2]Hay et al. (2014). *Quality of Life Research.*, 23(1):257-269. doi: 10.1007/s11136-013-0470-1

# PRO-CTCAE™:Content Validity

## Results:

- 78 symptomatic AEs identified from the more than 800 terms in the CTCAE lexicon; plain-language symptomatic AE terminologies developed[1]
- Each symptomatic AE term is assessed using 1 to 3 items[1]
- 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[2]

[1]Basch et al. (2014). *JNCI.*, 106(9). pii: dju244. doi: 10.1093/jnci/dju244

[2]Hay et al. (2014). *Quality of Life Research.*, 23(1):257-269. doi: 10.1007/s11136-013-0470-1

# PRO-CTCAE™ Attributes and Item Structures

| Frequency | Severity | Interference | Amount | Presence/Absence |
|---|---|---|---|---|
| In the last 7 days, how often did you have _____? | In the last 7 days, what was the severity of your _____ at its worst? | In the last 7 days, how much did _____ interfere with your usual or daily activities? | In the last 7 days, did you have any _____? | In the last 7 days, did you have any _____? |
| • Never<br>• Rarely<br>• Occasionally<br>• Frequently<br>• Almost constantly | • None<br>• Mild<br>• Moderate<br>• Severe<br>• Very severe | • Not at all<br>• A little bit<br>• Somewhat<br>• Quite a bit<br>• Very much | • Not at all<br>• A little bit<br>• Somewhat<br>• Quite a bit<br>• Very much | • No<br>• Yes |

- 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



For more information visit: http://healthcaredelivery.cancer.gov/pro-ctcae/

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Version date: 3/11/2020

# PRO-CTCAE™: Validity and Reliability

## Objective:

- Evaluate the quantitative measurement properties of PRO-CTCAE, specifically validity, reliability, sensitivity, and mode equivalence[1]

## 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



[1]Dueck AC et al. (2015). *JAMA Oncology.*, 1(8):1051-9. doi: 10.1001/jamaoncol.2015.2639

# PRO-CTCAE™: Validity and Reliability

## Results:

- PRO-CTCAE exhibits favorable validity, reliability, and responsiveness[1,2]
- 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

[1]Dueck AC et al. (2015). *JAMA Oncology.*, 1(8):1051-9. doi: 10.1001/jamaoncol.2015.2639
[2]Atkinson TM et al. (2018). *J Pain Symptom Manage.,*55(3):e3-e6. doi: 10.1016/j.jpainsymman.2017.10.024

# 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

[1]Dueck AC et al. (2015). *JAMA Oncology.*, 1(8):1051-9. doi: 10.1001/jamaoncol.2015.2639
[2]Atkinson TM et al. (2018). *J Pain Symptom Manage.,*55(3):e3-e6. doi: 10.1016/j.jpainsymman.2017.10.024

# 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)

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

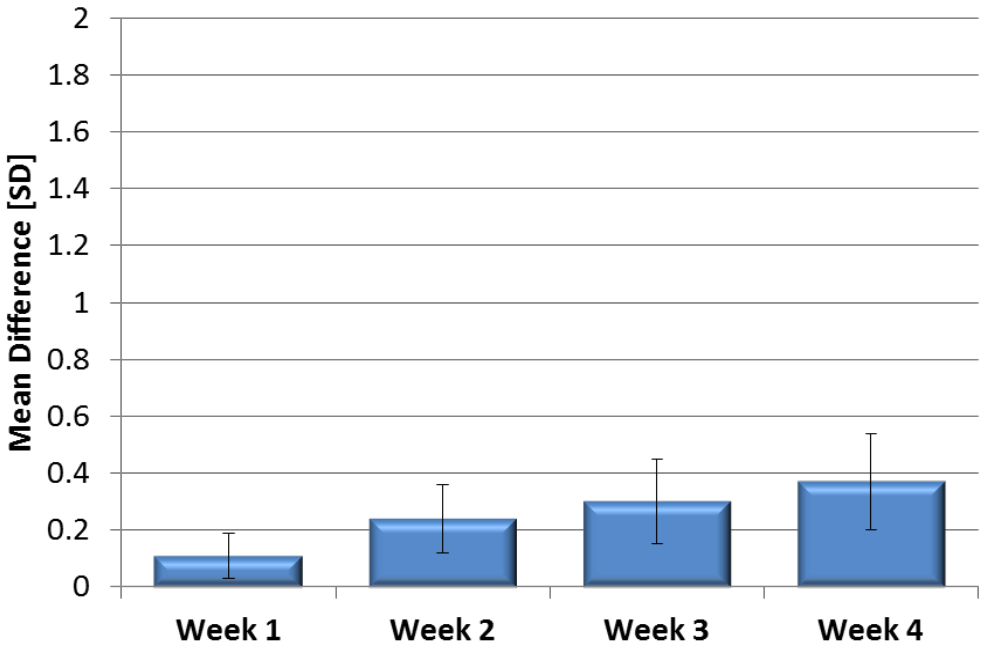
| | Median ICC (Range) | Median (range) between-mode item-level mean difference |
|---|---|---|
| Web vs IVRS | 0.78 (0.56 - 0.90) | -0.04 (-0.16 - 0.22) |
| Web vs paper | 0.81 (0.61 - 0.96) | -0.02 (-0.11 - 0.14) |
| IVRS vs paper | 0.78 (0.59 - 0.91) | 0.02 (-0.07 - 0.19) |


Bennett et al. (2016). *Health and Quality of Life Outcomes*.,19;14:24.doi: 10.1186/s12955-016-0426-6

# PRO-CTCAE™:Comparison of Recall Periods

- 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**






Mendoza et al. (2017). *Clinical Trials*., 14(3):255-263. doi: 10.1177/1740774517698645.

# PRO-CTCAE™ Development Team

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(awarded to Memorial Sloan Kettering Cancer Center)

# 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]

[1]Calvert et al. (2018). JAMA. 2018 Feb 6;319(5):483-494. doi: 10.1001/jama.2017.21903.
[2]Coens et al. (2020). Lancet Oncol. 21(2):e83-e96. doi: 10.1016/S1470-2045(19)30790-9.

# 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
  - 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

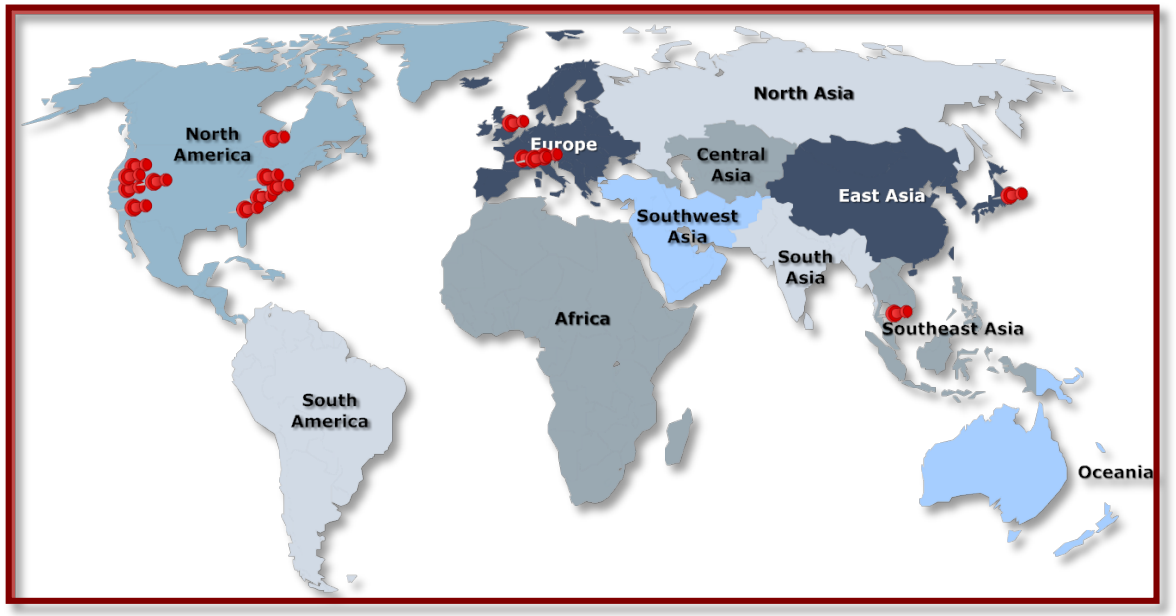
# Interpretation and Reporting

- 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 is needed before individual-level PRO-CTCAE scores can be used for clinical and protocol-specific decision-making (e.g. dose adjustments)

# PRO-CTCAE™
# Continued Development and Future Directions

# 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 25 languages, with 15 additional languages currently in development
- Pediatric module now available at the NCI website

# 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
  - Evaluate different approaches to patient-investigator grade reconciliation and to analyzing and representing PRO-CTCAE data
  - Adopters in surgical oncology, immuno-oncology, and radiation oncology testing items to expand the item library
  - Additional languages undergoing linguistic validation
  - Consortium established through Moonshot Funding (RFA-CA-17-052) to strengthen 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**