# Update on NCI's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events™ (PRO-CTCAE™)

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NIH NATIONAL CANCER INSTITUTE

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# Overview of Presentation

- History and Background

  Paul Jacobsen, PhD; Division of Cancer Control and Population Sciences; Healthcare Delivery Research Program

- Ongoing Development of PRO-CTCAE: Broadening Applicability and Interpretability in Cancer Clinical Trials

  Sandra Mitchell, PhD; Division of Cancer Control and Population Sciences; Outcomes Research Branch

- Inclusion of PRO-CTCAE in NCI-Sponsored Trials and Regulatory Considerations

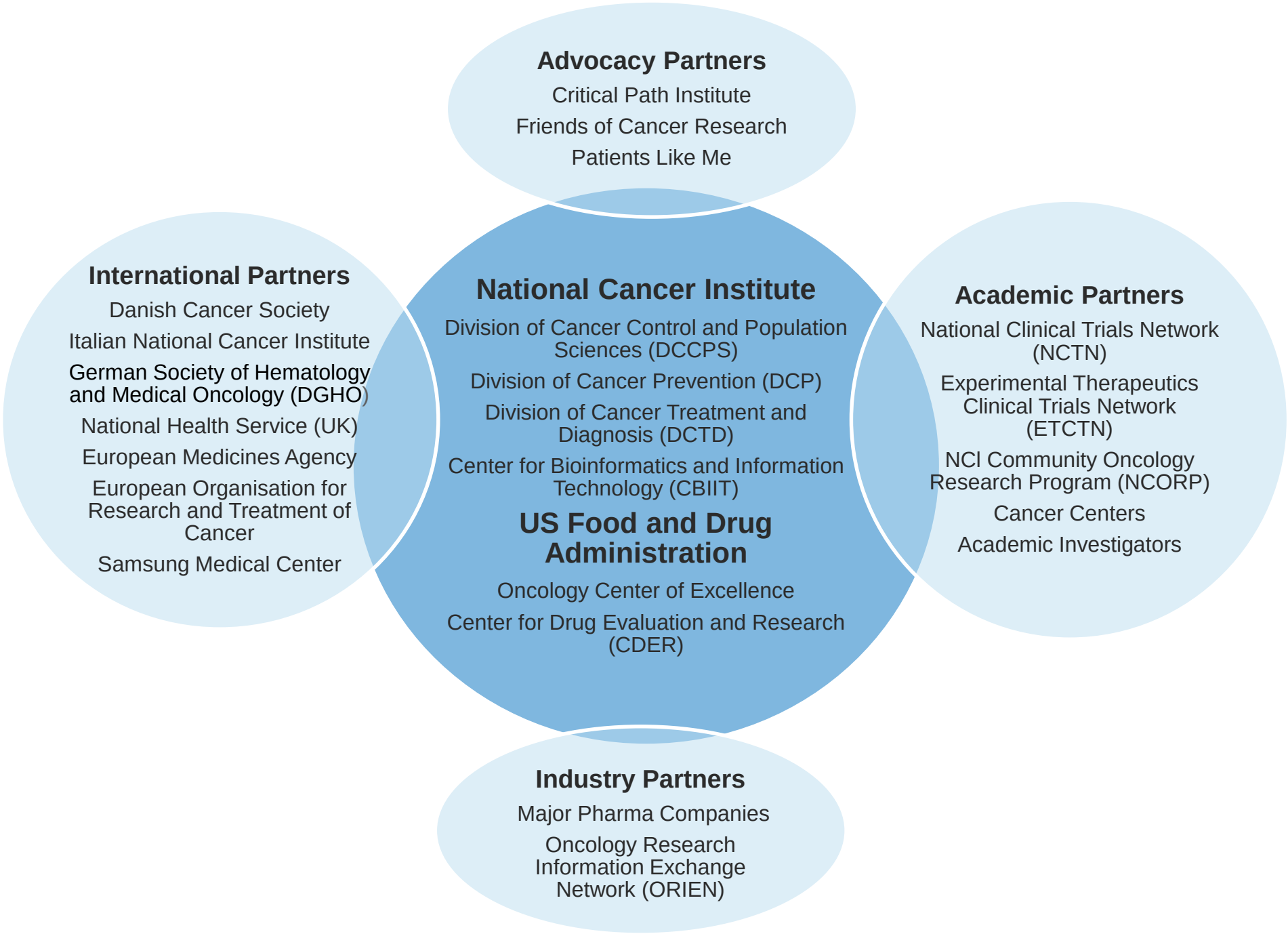
  Lori Minasian, MD; Division of Cancer Prevention

# PRO-CTCAE™: Rationale and Background

- ~10% of 800 adverse events listed in CTCAE are symptoms
- Validity of symptom reporting strengthened by inclusion of patient self-report
- PRO-CTCAE designed as companion to CTCAE to capture patient experience of symptomatic toxicities in cancer clinical trials
  - 78 symptomatic adverse events drawn from CTCAE
  - Customized surveys administered via paper or electronically
- As a measure of symptomatic adverse events, PRO-CTCAE captures information that in the future may have regulatory implications, and may become actionable at individual patient level
- Publicly available since April 2016

# PRO-CTCAE™: Timeline

- **2008-2015:** Contracts awarded for development and testing
  - Development and psychometric validation of the PRO-CTCAE item library (#HHSN261201000043C: Basch [2008-2013])
  - Examine feasibility, acceptability and resource requirements of PRO-CTCAE implementation in cooperative group trials (#HHSN261201000063C: Basch [2010-2015])
- **2011-present**: Early adopters in 12 countries (trialists in academia and industry)
  - 20 NCI-sponsored trials; >125 industry-sponsored studies
  - Population-based registry studies
  - Translations: Linguistic and psychometric validation in different languages for international trials


Advocacy Partners
Critical Path Institute
Friends of Cancer Research
Patients Like Me
International Partners
Danish Cancer Society
Italian National Cancer Institute
German Society of Hematology and Medical Oncology (DGHO)
National Health Service (UK)
European Medicines Agency
European Organisation for Research and Treatment of Cancer
Samsung Medical Center
National Cancer Institute
Division of Cancer Control and Population Sciences (DCCPS)
Division of Cancer Prevention (DCP)
Division of Cancer Treatment and Diagnosis (DCTD)
Center for Bioinformatics and Information Technology (CBIIT)
US Food and Drug Administration
Oncology Center of Excellence
Center for Drug Evaluation and Research (CDER)
Academic Partners
National Clinical Trials Network (NCTN)
Experimental Therapeutics Clinical Trials Network (ETCTN)
NCI Community Oncology Research Program (NCORP)
Cancer Centers
Academic Investigators
Industry Partners
Major Pharma Companies
Oncology Research Information Exchange Network (ORIEN)

# Ongoing Development of PRO-CTCAE: Broadening Applicability and Interpretability in Cancer Clinical Trials

*Sandra Mitchell, PhD*
*Research Scientist; Outcomes Research Branch*
*Healthcare Delivery Research Program*
*Division of Cancer Control and Population Sciences*

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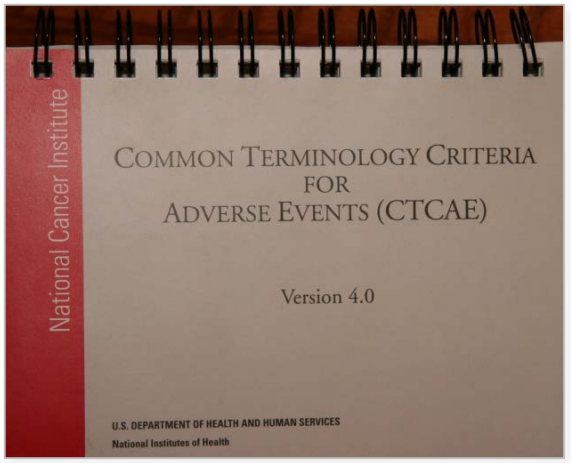
# Measuring Safety and Tolerability in Cancer Clinical Trials

- Fundamental to conclusions about the effectiveness of cancer therapies
  - Evaluated using **C**ommon **T**erminology **C**riteria for **A**dverse **E**vents (***CTCAE***)
- 10% of the 800 adverse events (AEs) listed in CTCAE are *symptoms*
  - Direct reporting by patients strengthens the captures of symptomatic adverse events[1]
  - Staff-based AE reporting occurs at clinic visits; symptomatic AEs occurring between visits may be missed




[1]Xiao et al. (2013). Comparison between patient-reported and clinician-observed symptoms in oncology. *Cancer Nurs.,*36(6):E1-E16

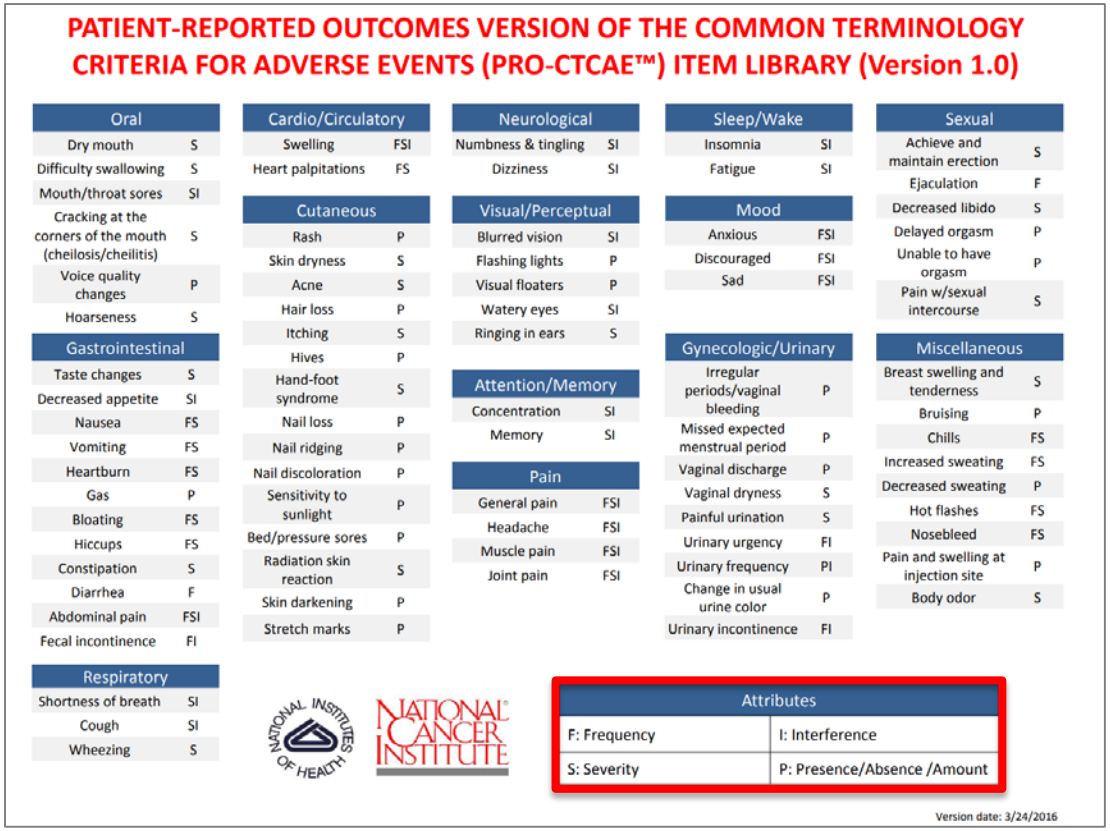
# Capturing Symptomatic Adverse Events in Cancer Clinical Trials

- Real-time ascertainment using patient-reported outcomes (PROs) can improve precision and reproducibility of symptomatic adverse event reporting

- **NCI's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)**
  - Developed to be used in conjunction with CTCAE to capture the patient experience of symptomatic toxicities in cancer clinical trials
  - Clinician CTCAE grades **bundle** frequency, severity and interference in the context of a clinical judgement
  - PRO-CTCAE items **distinguish** frequency, severity and interference

# PRO-CTCAE Measurement System

- 78 symptomatic adverse events drawn from CTCAE
- Investigators select PRO-CTCAE items that reflect anticipated toxicities of the therapy under study
- Conditional branching (skip patterns) within PRO-CTCAE items to reduce patient burden



**PATIENT-REPORTED OUTCOMES VERSION OF THE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (PRO-CTCAE™) ITEM LIBRARY (Version 1.0)**

| 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 | P |
| 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 |

| Gynecologic/Urinary | |
|---|---|
| Irregular periods/vaginal bleeding | P |
| Missed expected menstrual period | P |
| Vaginal discharge | P |
| Vaginal dryness | S |
| Painful urination | S |
| Urinary urgency | FI |
| Urinary frequency | PI |
| 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 /Amount |

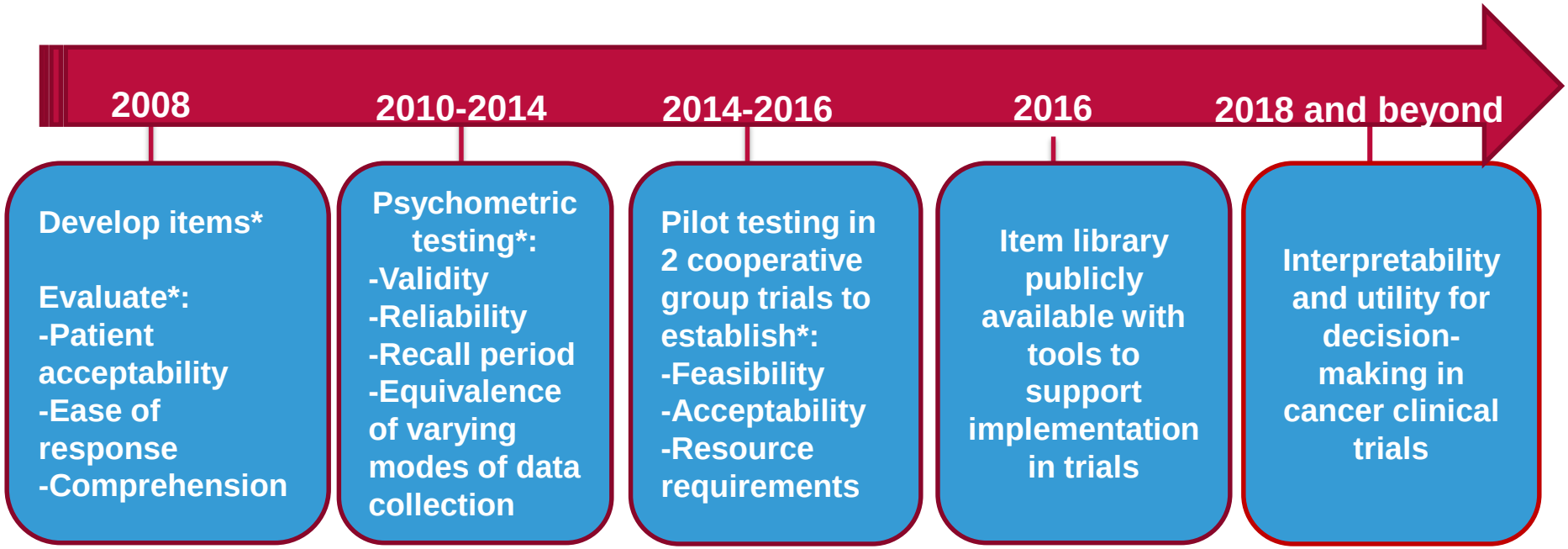
Version date: 3/24/2016

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

# CTCAE vs. PRO-CTCAE™ Item Structures

| CTCAE | | | | | |
|---|---|---|---|---|---|
| Adverse Event | Grade | | | | |
| | 1 | 2 | 3 | 4 | 5 |
| Mucositis oral | Asymptomatic or mild symptoms; intervention not indicated | Moderate pain; not interfering with oral intake; modified diet indicated | Severe pain; interfering with oral intake | Life-threatening consequences; urgent intervention indicated | - |

| PRO-CTCAE |
|---|
| Please think back over the past 7 days: |
| What was the severity of your MOUTH OR THROAT SORES at their WORST?<br>None / Mild / Moderate / Severe / Very severe |
| How much did MOUTH OR THROAT SORES interfere with your usual or daily activities?<br>Not at all / A little bit / Somewhat / Quite a bit / Very much |




- Psychometrically robust library of items
- Electronic system fits data collection smoothly into trials workflow and offers favorable user-experience
- Accommodates patients with limited English proficiency/digital literacy
- Supplies meaningful data to improve understanding of symptomatic AEs

**For more information, see bibliography of peer-reviewed publications in board briefing package*

# PRO-CTCAE Interpretation and Reporting

- PRO-CTCAE is designed to be used in conjunction with CTCAE
  - Provides complementary 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 to maximize interpretability and utility of results
- 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 are being studied
- Towards the future PRO-CTCAE may be able to inform clinician grades; various scientific initiatives underway with stakeholder participation

# Build a custom PRO-CTCAE survey using online Form Builder tool

Data, Tools, and Initiatives

Patient-Reported Outcomes Version of th

## PRO-CTCAE Instr

Use of the PRO-CTCAE is subject to NC
custom PRO-CTCAE form in any availab
cutting and pasting errors.

- Item Library (PDF, 179 KB) (English o
- English (PDF, 246 KB)
- Danish (PDF, 444 KB)
- German (PDF, 443 KB)
- Italian (PDF, 1.1 MB)
- Japanese (PDF, 672 KB)
- Korean (PDF, 708 KB)
- Spanish (PDF, 582 KB)
- In development and testing: Chines
  Swedish.

Certificates of translation are available.

*Studies using PRO-CTCAE:*

**>200 studies**

**PRO-CTCAE items needed**

**Oral**

- [x] Dry mouth
- [x] Difficulty swallowing
- [ ] Mouth/throat sores
- [ ] Cracking at the corners of the mouth (cheilosis/cheilitis)
- [ ] Voice quality changes
- [ ] Hoarseness

**Gastrointestinal**

- [ ] Taste changes
- [ ] Decreased appetite
- [x] Nausea
- [x] Vomiting
- [ ] Heartburn
- [ ] Gas
- [ ] Bloating
- [ ] Hiccups
- [ ] Constipation
- [ ] Diarrhea
- [ ] Abdominal pain
- [ ] Fecal incontinence

**Respiratory**

- [x] Shortness of breath
- [x] Cough
- [ ] Wheezing

**Cardio/Circulatory**

- [ ] Swelling
- [ ] Heart palpitations

**Cutaneous**

- [x] Rash
- [ ] Skin dryness
- [ ] Acne
- [ ] Hair loss
- [ ] Itching
- [ ] Hives
- [ ] Hand-foot syndrome
- [ ] Nail loss
- [ ] Nail ridging
- [ ] Nail discoloration
- [ ] Sensitivity to sunlight
- [ ] Bed/pressure sores
- [ ] Radiation skin reaction
- [ ] Skin darkening
- [ ] Stretch marks

**Neurological**

- [ ] Numbness & tingling
- [x] Dizziness

**Visual/Perceptual**

- [ ] Blurred vision
- [ ] Flashing lights
- [ ] Visual floaters
- [ ] Watery eyes
- [ ] Ringing in ears

**Attention/Memory**

- [ ] Concentration
- [ ] Memory

**Pain**

- [x] General pain
- [x] Headache
- [ ] Muscle pain
- [x] Joint pain

**Sleep/Wake**

- [ ] Insomnia
- [ ] Fatigue

**Mood**

- [x] Anxious
- [ ] Discouraged
- [ ] Sad

**Gynecologic/Urinary**

- [ ] Irregular periods/vaginal bleeding
- [ ] Missed expected menstrual period
- [ ] Vaginal discharge
- [ ] Vaginal dryness
- [ ] Painful urination
- [ ] Urinary urgency
- [ ] Urinary frequency
- [ ] Change in usual urine color
- [ ] Urinary incontinence

**Sexual**

- [ ] Achieve and maintain erection
- [ ] Ejaculation
- [ ] Decreased libido
- [ ] Delayed orgasm
- [ ] Unable to have orgasm
- [ ] Pain w/sexual intercourse

**Miscellaneous**

- [ ] Breast swelling and tenderness
- [ ] Bruising
- [ ] Chills
- [ ] Increased sweating
- [ ] Decreased sweating
- [ ] Hot flashes
- [ ] Nosebleed
- [ ] Pain and swelling at injection site
- [ ] Body odor

Download form in: English | Danish | German | Japanese | Spanish | Italian | Korean

# Linguistic Validation to Support International Trials*

| Currently Available | Public Release in January 2018* | Anticipated Release in August 2018 |
|---|---|---|
| English | Chinese (traditional) | Chinese (simplified)* |
| Spanish | Russian | Malay* |
| German | French | Portuguese* |
| Japanese | Hungarian | Dutch* |
| Danish | Czech | Romanian† |
| Korean | Swedish | Turkish† |
| Italian | Polish | |
| | Greek | |

*Funded by CRADAs with Genentech/Roche of approximately 2.5 Million

†Funded by CRADA with BMS of approximately 200K

# Ongoing Work: Interpretability and Utility

- Interpretation and clinical utility of PRO-CTCAE still evolving
  - Implementation in early phase studies and randomized trials
  - Anticipate future use in novel trial designs
- Enhance access, interpretability and utility of PRO-CTCAE
  - Responsiveness, minimal clinically important difference, relationship among the attributes, and empirically-derived interpretive cut-points
  - Adopters in surgical oncology, immuno-oncology, and radiation oncology testing items to expand the item library
  - Technologies to optimize acceptability of electronic data capture for persons with lower literacy and limited digital literacy
  - Pediatric PRO-CTCAE in psychometric testing
  - Moonshot RFA (RFA-CA-17-052) to strengthen the analysis and interpretation of PRO-CTCAE and CTCAE data together to improve our understanding of treatment tolerability (FY 2018 set-aside: $3.25 million)

# Inclusion of PRO-CTCAE in NCI-Sponsored Clinical Trials and Regulatory Considerations

Lori Minasian, M.D., FACP
Deputy Director
NCI Division of Cancer Prevention

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# Vision for PRO-CTCAE in NCI Clinical Trials

- To capture patients' perception of symptomatic adverse events in a manner complementary to clinician graded adverse events
  - Improve the identification of tolerability for cancer treatment regimens and cancer prevention/control interventions
- To efficiently incorporate PRO-CTCAE into the operational collection of clinical trial data
  - Streamline data collection for patients and site staff
  - Facilitate analysis of PRO-CTCAE data by housing data within the existing clinical trials database
- To enhance patient participation during cancer clinical trials

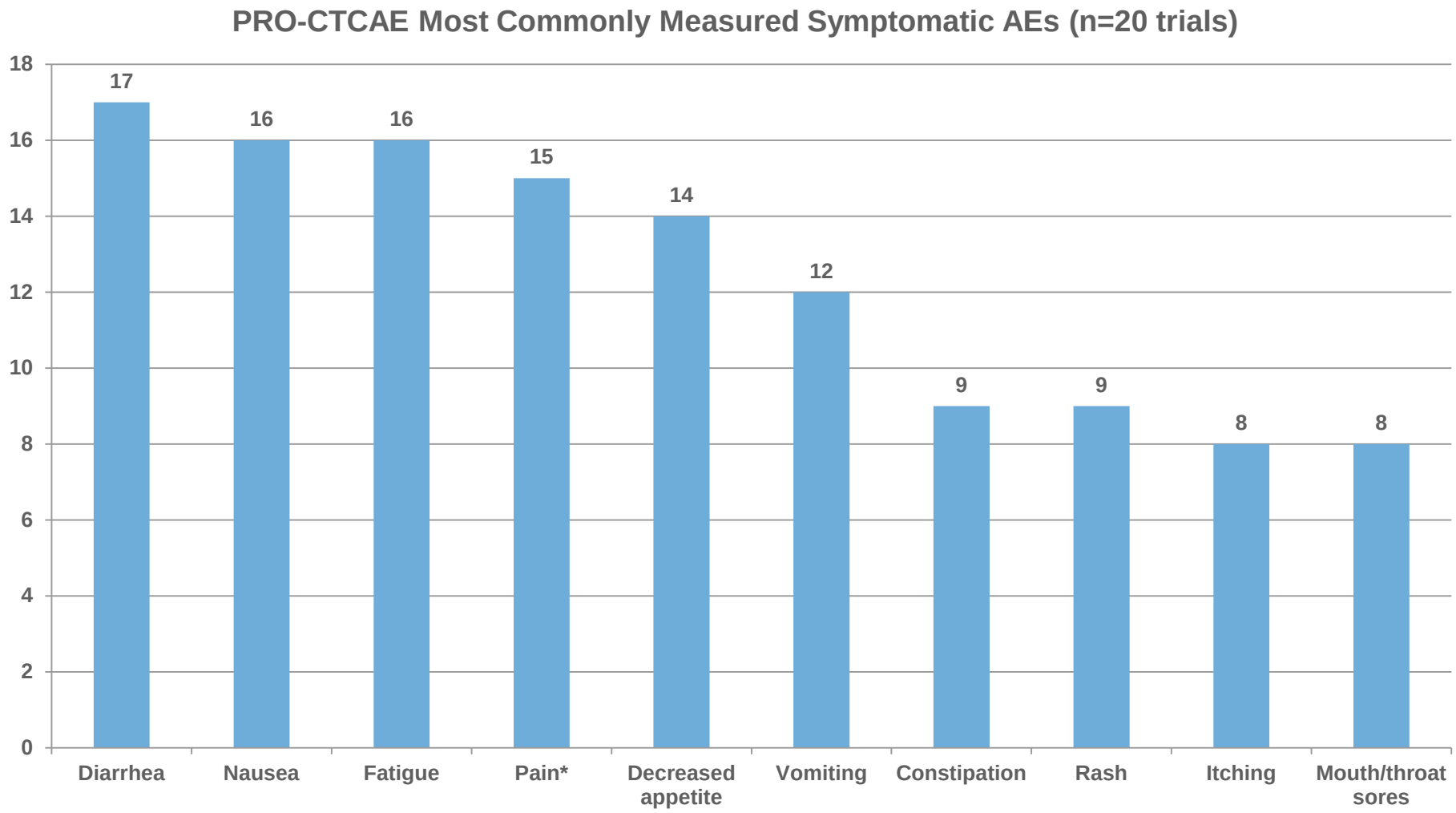
# NCI-Sponsored Trials With PRO-CTCAE (n=20)*

| Phase | Number of Trials |
|---|---|
| Phase I | 1 |
| Phase II | 8 |
| Phase II/III | 1 |
| Phase III | 10 |
| **Total** | **20** |

| Current Status | Number of Trials |
|---|---|
| Active | 13 |
| Closed to accrual | 4 |
| Closed to accrual & treatment | 1 |
| Complete | 1 |
| FDAAA/IRB completed | 1 |
| **Total** | **20** |

*5 additional trials that include PRO-CTCAE are in review; 3 active trials are in the process of adding PRO-CTCAE as an amendment

# NCI-Sponsored Trials With PRO-CTCAE (n=20)



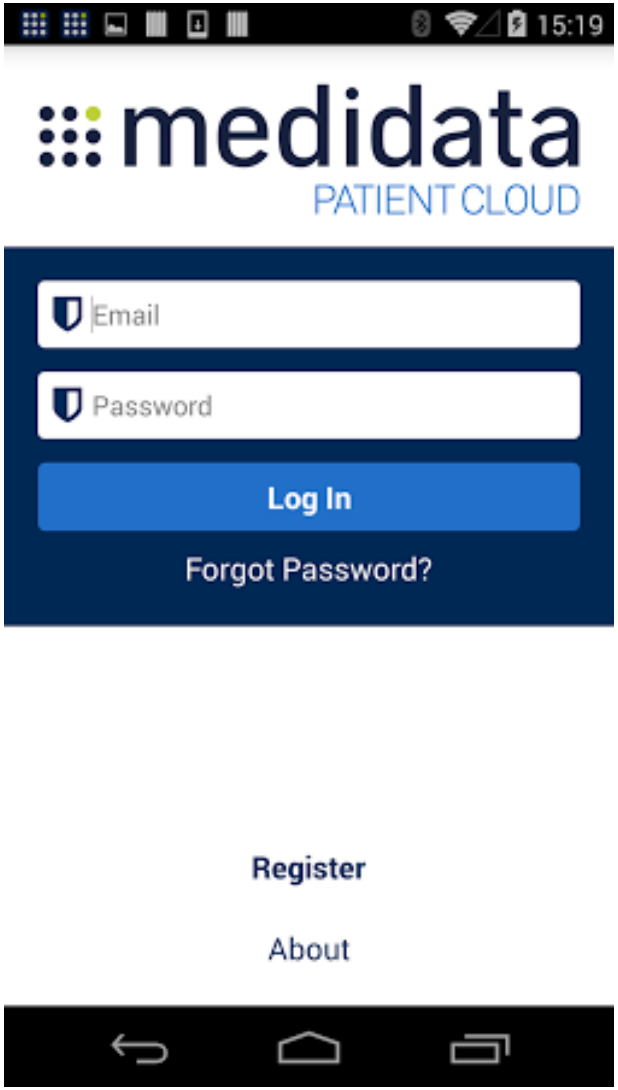

*Pain: Including headache, muscle pain, joint pain

# Electronic Data Collection for PRO-CTCAE

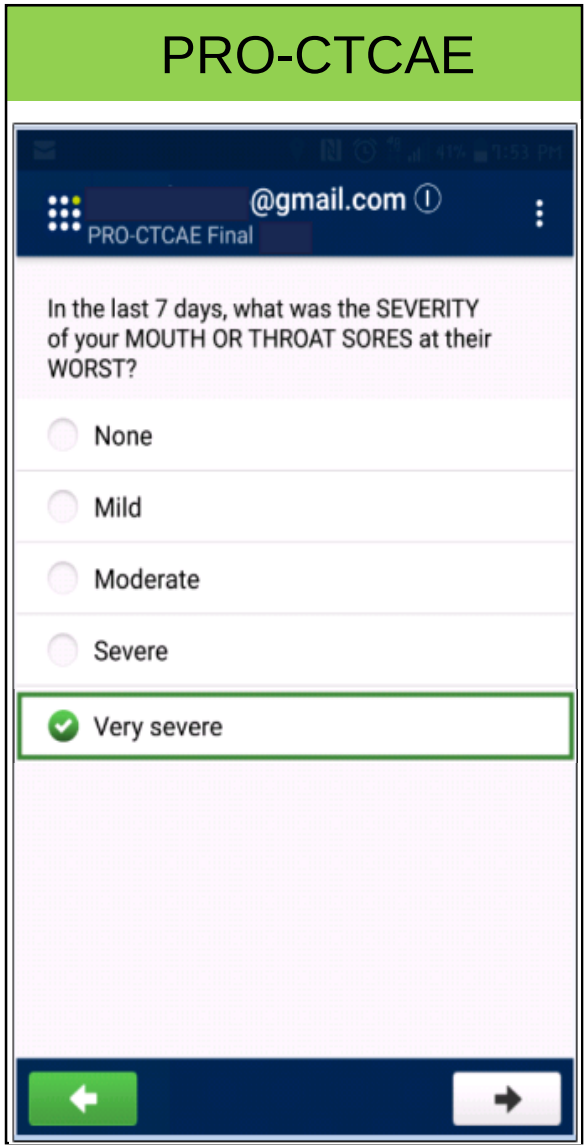
- Prototype system developed to capture PRO-CTCAE data electronically in NCI-sponsored feasibility studies (2012-2016)
  - System not scalable for NCI network trials
  - PRO-CTCAE data housed independently from clinical trials data
- August 2016: Implementation of medidata Rave® ePRO module
  - Allows patients to respond on devices that they already are using
  - Reduces missing data with patient responding directly from their mobile devices into clinical trial database
  - Eliminates site staff provision of questionnaires to patients and the subsequent data entry of patient responses
- August 2017: Trial-specific custom PRO-CTCAE surveys available to NCI network investigators within medidata Rave

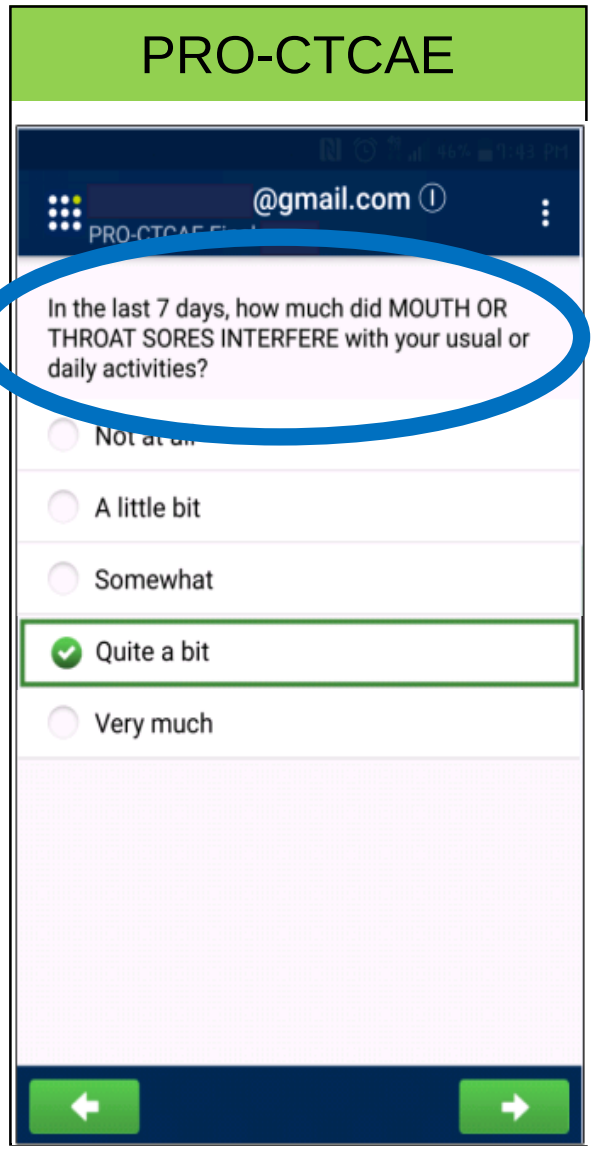
# Patient Cloud ePRO Overview

- What is Patient Cloud ePRO?
  - A mobile app to collect patient self report and transfer data medidata Clinical Cloud
  - Allows multiple different PRO tools (diaries, questionnaires) to be used, facilitating ease of use
  - Available for Android and iOS mobile devices



# Patient Cloud ePRO Overview



# Regulatory Issues: PRO-CTCAE in Clinical Trials

- Active collaborations with FDA, Critical Path Institute, Friends of Cancer Research
  - Critical Path-FDA Clinical Outcomes Assessment Annual Meetings focused on PRO-CTCAE (2016 and 2017)
  - FDA Longitudinal Data Analysis Workshop (2017)
  - PRO-CTCAE Industry Working Group (ongoing)
  - Friends of Cancer Research Annual Meetings (2013, 2015)

- FDA and NCI staff hold regular meetings
  - Data standards
  - Interpretability
  - Regulatory concerns: Safety signal or not?

# Regulatory Issues: Safety Reporting

- FDA, NCI and OHRP staff met in April 2017
  - Focus on implications of PRO-CTCAE for clinical review, IND safety reporting and clinical site inspections
  - Outcomes[1]:
    - PRO-CTCAE data analyzed in aggregate at the trial level
    - No expectation that PRO-CTCAE data be reported as safety data
    - PRO-CTCAE data are complementary to clinician CTCAE data, but are also expected to differ from clinician grades (not a discrepancy for site inspections)

[1]Kim et al. Use of PRO measures to inform tolerability in oncology trials: Implications for clinical review, IND safety reporting and clinical site inspections. *Clinical Cancer Research*. *In Press*.

# Current Opportunities: Methods for Analysis

- *CTCAE data*: Individual patient data is analyzed in real time for safety and is actionable
  - CTCAE data reflects the most severe toxicity in a cycle
    - Safety signal (dose reductions, modifications, discontinuation)
  - Typical data tables do not provide information on onset, resolution and trajectory over time
- *PRO-CTCAE data*: Data analyzed in aggregate at the trial level, can provide information about trajectory over time, but does not result in a dose modification at the individual patient level
  - PRO-CTCAE
    - Potential signal for tolerability
    - Additional work needed to effectively analyze PRO-CTCAE and CTCAE data together

# Moonshot RFA-CA-17-052

(applications due January 17, 2018; letter of intent requested 30 days prior)


- Analyzing and Interpreting Clinician and Patient Adverse Event Data to Better Understand Tolerability
  - Using PRO-CTCAE with CTCAE data and other clinically relevant trial data to determine tolerability
  - Evaluating associations between baseline symptoms (with pharmacologic or other laboratory data) and emerging symptomatic AEs
  - Using different approaches to address missing PRO-CTCAE data, e.g., characterizing missingness, gauging bias
- Create a consortium to share analytic approaches
  - Biostatisticians, data scientists, investigators with PRO measurement expertise, and cancer clinical trialists
  - Patient advocates, regulatory experts, NCI staff



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