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

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Healthcare Delivery Research Program
Division of Cancer Control and Population Sciences

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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
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
Measuring Safety and Tolerability in Cancer Clinical Trials

• Fundamental to conclusions about the effectiveness of cancer therapies
  • Evaluated using Common Terminology Criteria for Adverse Events (CTCAE)

• 10% of the 800 adverse events (AEs) listed in CTCAE are symptoms
  • Direct reporting by patients strengthens the captures of symptomatic adverse events
  • Staff-based AE reporting occurs at clinic visits; symptomatic AEs occurring between visits may be missed

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

For more information about PRO-CTCAE visit: https://healthcaredelivery.cancer.gov/pro-ctcae
## CTCAE vs. PRO-CTCAE™ Item Structures

<table>
<thead>
<tr>
<th>CTCAE</th>
<th>PRO-CTCAE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event</strong></td>
<td><strong>Grade</strong></td>
</tr>
<tr>
<td>Mucositis oral</td>
<td>1: 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
Develop items*
Evaluate*:
- Patient acceptability
- Ease of response
- Comprehension

Psychometric testing*:
- Validity
- Reliability
- Recall period
- Equivalence of varying modes of data collection

Pilot testing in 2 cooperative group trials to establish*:
- Feasibility
- Acceptability
- Resource requirements

Item library publicly available with tools to support implementation in trials

Interpretability and utility for decision-making in cancer clinical trials

- 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 FormBuilder tool.

Studies using PRO-CTCAE: >200 studies

Average number of visits to the PRO-CTCAE Home Page: 671 per month (range 374-861 visits per month)

Average number of visits to the PRO-CTCAE Instrument Page and FormBuilder: 323 per month (range 162-533 visits per month)

PRO-CTCAE Instrument
Use of the PRO-CTCAE is subject to no custom PRO-CTCAE form in any available cutting and pasting errors.

- Item Library (PDF, 179 KB) (English or PRO-CTCAE)
- Danish (PDF, 444 KB) (German, French, or Spanish)
- Italian (PDF, 1.1 MB)
- Japanese (PDF, 672 KB)
- Korean (PDF, 708 KB)
- Spanish (PDF, 582 KB)
- In development and testing: Chinese, Swedish.

Certificates of translation are available.
# Linguistic Validation to Support International Trials*

<table>
<thead>
<tr>
<th>Currently Available</th>
<th>Public Release in January 2018*</th>
<th>Anticipated Release in August 2018</th>
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<tbody>
<tr>
<td>English</td>
<td>Chinese (traditional)</td>
<td>Chinese (simplified)*</td>
</tr>
<tr>
<td>Spanish</td>
<td>Russian</td>
<td>Malay*</td>
</tr>
<tr>
<td>German</td>
<td>French</td>
<td>Portuguese*</td>
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<tr>
<td>Japanese</td>
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<tr>
<td>Greek</td>
<td></td>
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</tr>
</tbody>
</table>

*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
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)*

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number of Trials</th>
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<tbody>
<tr>
<td>Phase I</td>
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</tr>
<tr>
<td>Phase II</td>
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<tr>
<td>Phase II/III</td>
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<tr>
<td>Phase III</td>
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<tr>
<td><strong>Total</strong></td>
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<table>
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<tr>
<th>Current Status</th>
<th>Number of Trials</th>
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<td>Closed to accrual</td>
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<tr>
<td>Closed to accrual &amp; treatment</td>
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</tr>
<tr>
<td>Complete</td>
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</tr>
<tr>
<td>FDAAA/IRB completed</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>20</strong></td>
</tr>
</tbody>
</table>

*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)

PRO-CTCAE Most Commonly Measured Symptomatic AEs (n=20 trials)

- Diarrhea: 17
- Nausea: 16
- Fatigue: 16
- Pain*: 15
- Decreased appetite: 14
- Vomiting: 12
- Constipation: 9
- Rash: 9
- Itching: 8
- Mouth/throat sores: 8

*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
In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?

- None
- Mild
- Moderate
- Severe

- Very severe

In the last 7 days, 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
Regulatory Issues: PRO-CTCAE in Clinical Trials

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

• 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)

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
• 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