PRO-CTCAE™:

PATIENT-REPORTED OUTCOMES VERSION OF CTCAE

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Disclosures

- I work for the USA Federal Government
- I have no financial conflicts to disclose
- Presenting on behalf of the NCI PRO-CTCAE Scientific Leadership Team

Outline of Talk

- Psychometric development for PRO-CTCAE™
- Describe initial principles for use
- Identify differences
  - between HRQOL tools and toxicity reporting

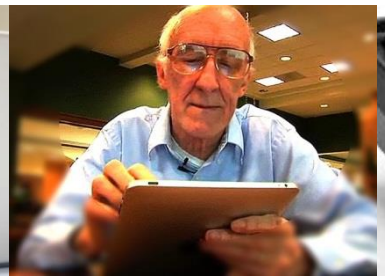
What is PRO-CTCAE™?

- PRO-CTCAE is designed for patient reporting of symptomatic adverse events
- PRO-CTCAE is an item bank of questions
  - Derived from the CTCAE adverse event items
  - Complimentary to CTCAE (and to be used with)
- PRO-CTCAE is ONLY for descriptive reporting
  - Not ready for clinical and protocol specific decision-making based upon individual PRO-CTCAE scores

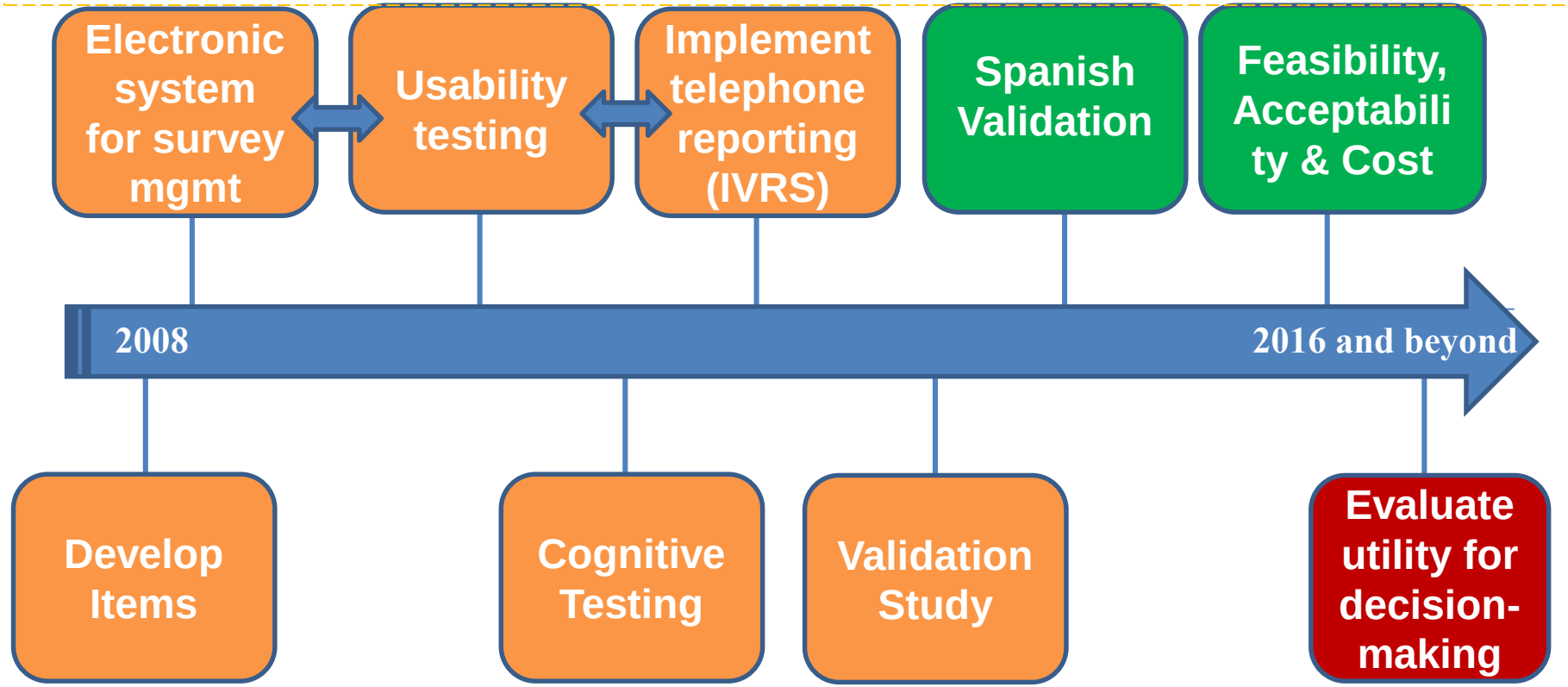
PRO-CTCAE Measurement System

1. Symptom Library	2. System for Survey Administration
• 78 symptomatic adverse events drawn from CTCAE • PRO-CTCAE questions evaluate symptom occurrence, frequency, severity, and interference	• Web-based system to customize surveys and manage survey administration • Patient responds to surveys using web, tablet or interactive voice response (IVRS) telephone system • Conditional branching (skip patterns) • Write-ins with automatic mapping to standardized terminology

For more information, visit: http://outcomes.cancer.gov/tools/pro-ctcae.html


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



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PRO-CTCAE Content Validity

- 78 symptomatic AEs identified from ~800 CTCAE terms for patient self-reporting
  - Plain-language AE terms identified
- Each symptomatic AE has 1 to 3 items[1]
  - Frequency, severity, interference w/ activities
- Content validity established during three interview rounds with semi-structured interview using structured and open-ended probes (N=127)[2]
  - 63/80 symptom terms generated no cognitive difficulties; 17 modified and re-tested without further difficulties

[1]Basch et al., (2014). Development of the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *Journal of the National Cancer Institute*, 106(9). pii: dju244

[2]Hay et al. (2014). Cognitive interviewing of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) to support content validity. *Quality of Life Research,* 23(1):257-269

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

Dimensions	
F: Frequency	I: Interference
S: Severity	P: Presence/Absence /Amount

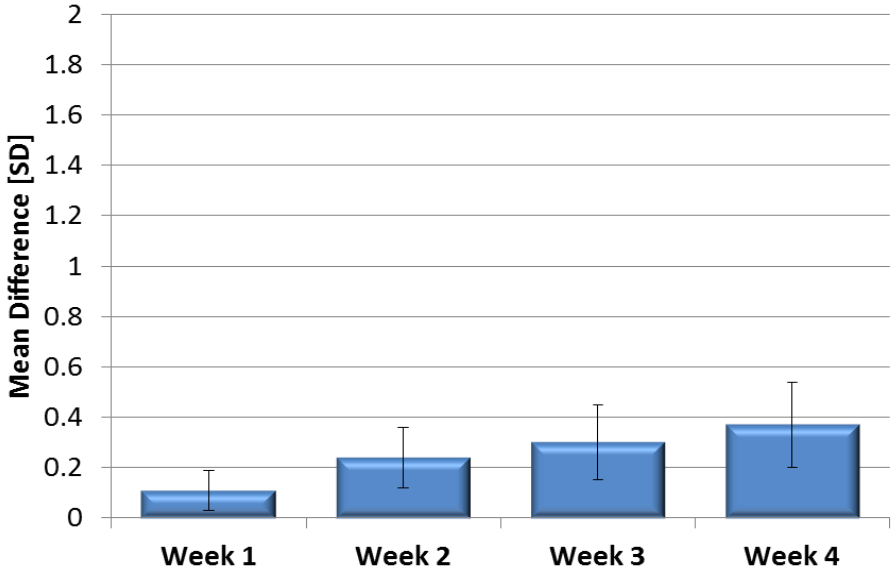
PRO-CTCAE Validity and Reliability

- Results demonstrate favorable validity, reliability, and responsiveness of PRO-CTCAE in a large, heterogeneous sample of patients undergoing cancer treatment (n=940)[1]
  - Most PRO-CTCAE items (119/124) reached a statistically significant ($p<0.05$) and meaningful effect size on one or more validity criteria
  - Majority of the items tested (n=27 items) exhibited acceptable test-retest reliability
  - All tested items (n=27 items) were sensitive to differences between groups

Validity and reliability of the U.S. National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *JAMA Oncology*, Epub ahead of print.

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



Recall Period	Effect Size of the Difference (compared to max. daily score within that period)
7 day	-0.2
14 day	-0.31
21 day	-0.39
Past month	-0.40

Mendoza et al. Evaluation of different recall periods for the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Manuscript in preparation for *Clinical Trials*.

Timeframe for Assessments

- Recall period is 7 days
  - Anticipate weekly reporting
  - Currently, data to demonstrate ~ 90% compliance for weekly reporting up to 20 weeks with reminders.
  - Baseline and off-study assessment are essential
  - Balance number of items asked and frequency of time for assessments with data quality

- If asking questions with an interval of longer than one week, the recall period remains the last 7 days

Mode Equivalence

- N=112 patients completed 28 PRO-CTCAE items (14 symptomatic AEs) 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)

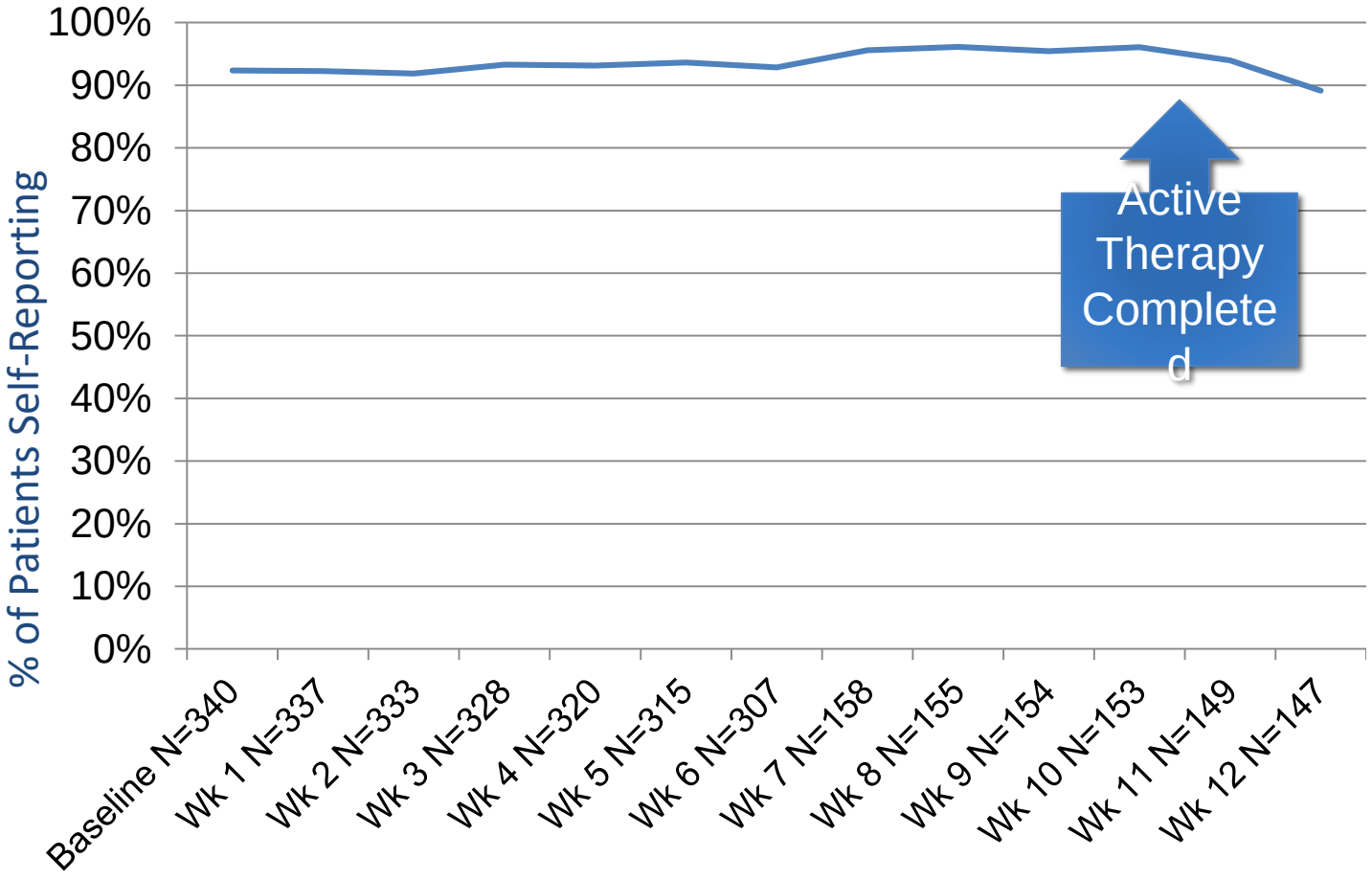
Bennett et al. (2016). *Health and Quality of Life Outcomes.* E Pub ahead of print.

Technology May Improve Data Collection

- Electronic administration reduces the number of items that must be asked of patients
  - Conditional branching
  - Computer adaptive testing
- Technology has enabled data collection to be more efficient, customized, mobile, and responsive
  - Smart phone/hand-held devices/Interactive Voice Response (IVRS) for data collection
  - Customize time of day for assessment, text size on screen, and mode of administration
  - Reminders to patients and staff for missed surveys
  - Eliminate need for data entry
  - Mobile devices may improve engagement

Example from Actual Trial: Compliance over Time

Weekly reporting from home via Web or IVRS (patient choice), with central monitoring and backup human telephone calls



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Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)

This site was designed to provide you with information about the PRO-CTCAE, a patient-reported outcome measurement system developed by the National Cancer Institute to capture symptomatic adverse events in patients on cancer clinical trials.

The site includes an overview of the methods used to develop this measurement system, and resources and references for further information.

Toxicity Reporting & PRO-CTCAE

- Toxicity Reporting
  - Clinician assesses adverse events and grade events
  - Action is taken based upon protocol specific instructions for the purpose of preventing or reducing harm
  - Events reviewed in real time and study design may be modified
  - Each event is reported and analyzed independently

- PRO-CTCAE
  - Patient answers separate questions about occurrence of event
  - If event occurs, answer questions about frequency, severity or interference
  - No protocol directed modifications based only on patient reports
  - Each event evaluated individually (No summary score)

CTCAE Use Within Clinical Trials

- Protocol parameters
  - Patient Eligibility
  - Dose Limiting Toxicity (DLT)
  - Maximum Tolerated Dose (MTD) determination
  - Dose Modification
- Recommended Phase 2 dose
- Reporting of both routine adverse events and serious adverse events (SAE)
- Monitor safety data and regulatory reporting

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? 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

PRO-CTCAE Score vs. CTCAE Grade

- PRO-CTCAE responses are scored from 0 to 4
  - Up to three questions per AE Item
    - Frequency, Severity, Interference

- Clinician CTCAE Grade
  - Bundles the constructs of severity, frequency and interference
  - Grading dependent upon clinician judgement of medical significance

- Clinician Grade ≠ PRO-CTCAE Score
  - One grade by clinician
  - Up to three patient reported scores per Item
  - CTCAE Grade 4 does not exist for most of the PRO-CTCAE items

HRQOL ≠ Toxicity Reporting

- HRQOL
  - Questions designed to address overall effects of cancer and its treatment
  - Patient answers questions in real time
  - Responses evaluated by study at the completion of the study
  - Tools are designed to provide a summary score

- Toxicity Reporting
  - Clinician assesses adverse events for patient safety
  - Action is taken specifically to reducing further harm
  - Events reviewed in real time and study design may be modified
  - Each event is reported independently

Key Points

- Different tools used for different purposes
- HRQOL provides an assessment for multiple different domains on how a patient experiences the combination of cancer, its treatment and related effects.
- Toxicity reporting is specific to safety and patients may not be aware of what is treatment related or cancer related.

Key Points

- PRO-CTCAE is a new tool:
- Derived from clinician rated CTCAE for the purpose of refining the understanding of adverse events as a consequence of treatment.
- Clinician graded CTCAE remains standard for protocol directed action specific individual adverse events
- PRO-CTCAE provides descriptive information to compliment clinician reporting
- Much more work is needed to understand how best to use PRO-CTCAE data.

Ongoing Work

- Responsiveness, minimal clinically important difference, cut-points, relationship among the attributes
- Several languages in development/validation, including Chinese, Korean, Italian, French, Swedish, Dutch, and Danish
- Evaluate different approaches to patient-investigator grade reconciliation and to analyzing and representing PRO-CTCAE data

NCI PRO-CTCAE Study Group

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