

Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events

PRO-CTCAE

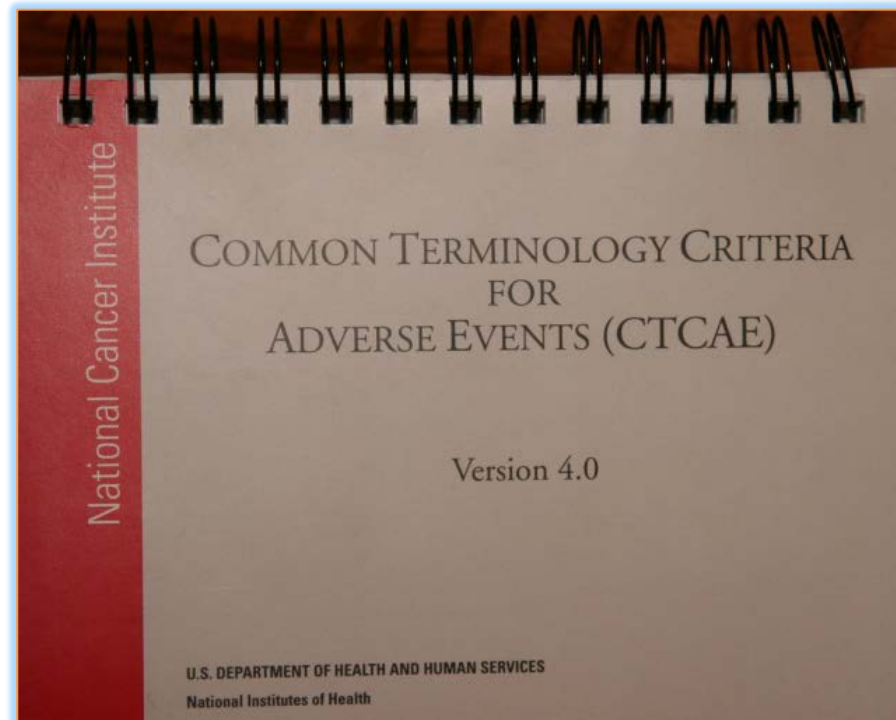
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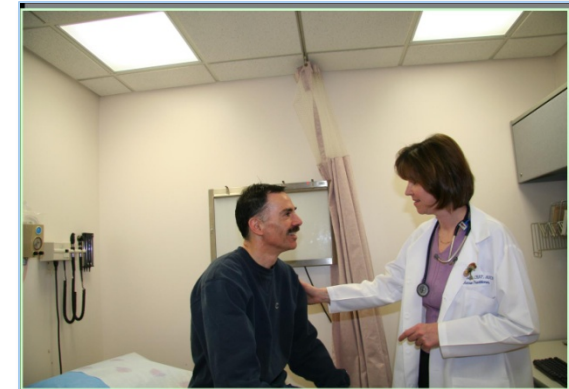
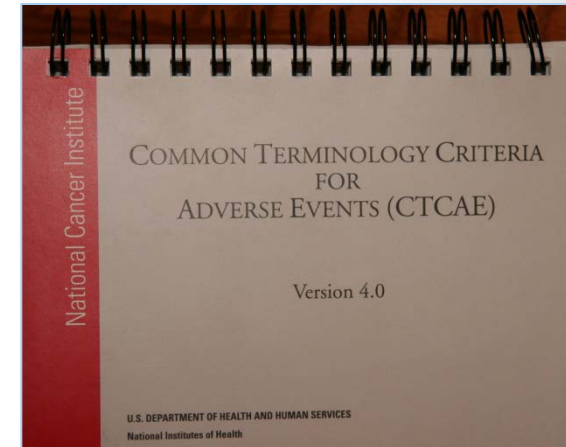
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Presentation to Clinical Trials Advisory Committee: November 6, 2013

- Treatment-related toxicity (safety and tolerability)
 - Fundamental outcome when drawing conclusions about therapeutic effectiveness, including comparative effectiveness
 - Currently evaluated by clinicians using **Common Terminology Criteria for Adverse Events (CTCAE)**



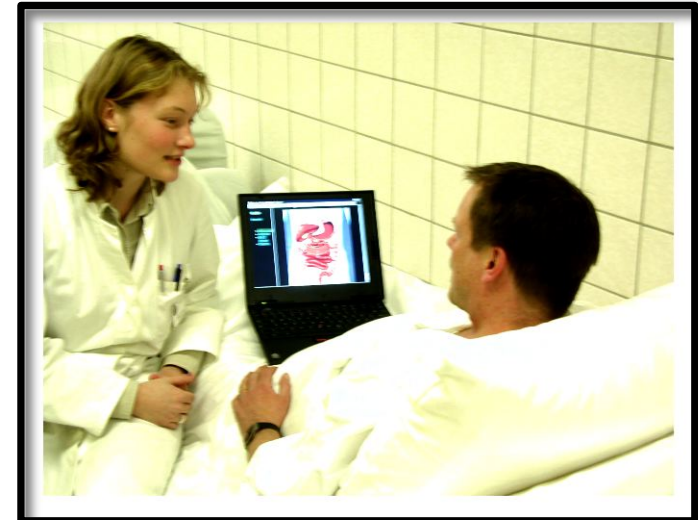
- 1 of 8 of the adverse events listed in CTCAE is a symptom outcome
 - Validity of reporting symptom outcomes is eroded when those reports are filtered through research staff and clinicians¹
 - Staff-based adverse event reporting occurs at clinic visits; adverse events that occur between visits may be missed
- Real-time ascertainment of symptomatic adverse events using PROs could improve the precision and reproducibility of adverse event reporting
- PRO reporting of symptomatic toxicities is valued by trialists²



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

²Bruner et al. (2011). Stakeholder Perspectives on Implementing the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *Translational Behavioral Medicine: Practice, Policy, Research*, 1 (1), 110-122.

- **PRO-CTCAE** is a patient-reported outcome (PRO) measure that ascertains in real time the presence, severity and interference of symptoms experienced by patients participating in cancer clinical trials
- Co-funding and Strategic Oversight
 - DCCPS
 - DCP
 - DCTD
 - CBIIT
- Contracts awarded to Memorial Sloan-Kettering Cancer Center: Ethan Basch, PI





NCI PRO-CTCAE Study Group

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- Organizational Affiliations: NCI Community Cancer Centers Program (NCCCP), RTOG, Alliance, FDA
- We gratefully acknowledge our study participants and patient representatives!

PRO-CTCAE Measurement System

1. Symptom Library

- 78 symptomatic adverse events drawn from CTCAE
- PRO-CTCAE questions evaluate symptom occurrence, frequency, severity, and interference

2. System for Survey Administration

- 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





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 Symptom Library

Neuro

- Numbness & Tingling*
- Tremors
- Dizziness

Attention/Memory

- Concentration*
- Memory

Sleep/Wake

- Insomnia*
- Fatigue*

Gynecologic/Urinary

- Vaginal bleeding
- Missed menstrual periods
- Vaginal discharge
- Vaginal dryness
- Painful urination
- Urinary urgency
- Urinary frequency
- Change in usual urine color
- Urinary Incontinence

Sexual

- Achieve and maintain erection
- Ejaculation
- Desire
- Orgasm
- Pain w/sexual intercourse

Mood

- Anxious*
- Discouraged
- Sad*

Pain

- General pain*
- Headache*
- Muscle pain
- Joint pain

Miscellaneous

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

Cutaneous

- Rash*
- Skin dryness
- Acne
- Hair Loss*
- Hand-foot syndrome
- Hives
- Itching
- Nail loss
- Nail ridging
- Nail discoloration
- Sensitivity to sunlight
- Pressure Sores
- Radiation skin reaction
- Skin darkening
- Stretch marks

Oral

- Dry mouth*
- Difficulty swallowing
- Mouth/throat sores*
- Cracking at the corners of the mouth (cheliosis)
- Voice quality changes/
- Hoarseness

Gastro-Intestinal

- Taste Changes*
- Decreased appetite*
- Nausea*
- Vomiting*
- Heartburn
- Gas
- Bloating
- Hiccups
- Constipation*
- Diarrhea*
- Abdominal pain
- Fecal Incontinence

Respiratory

- Shortness of
- Breath*
- Cough
- Wheezing

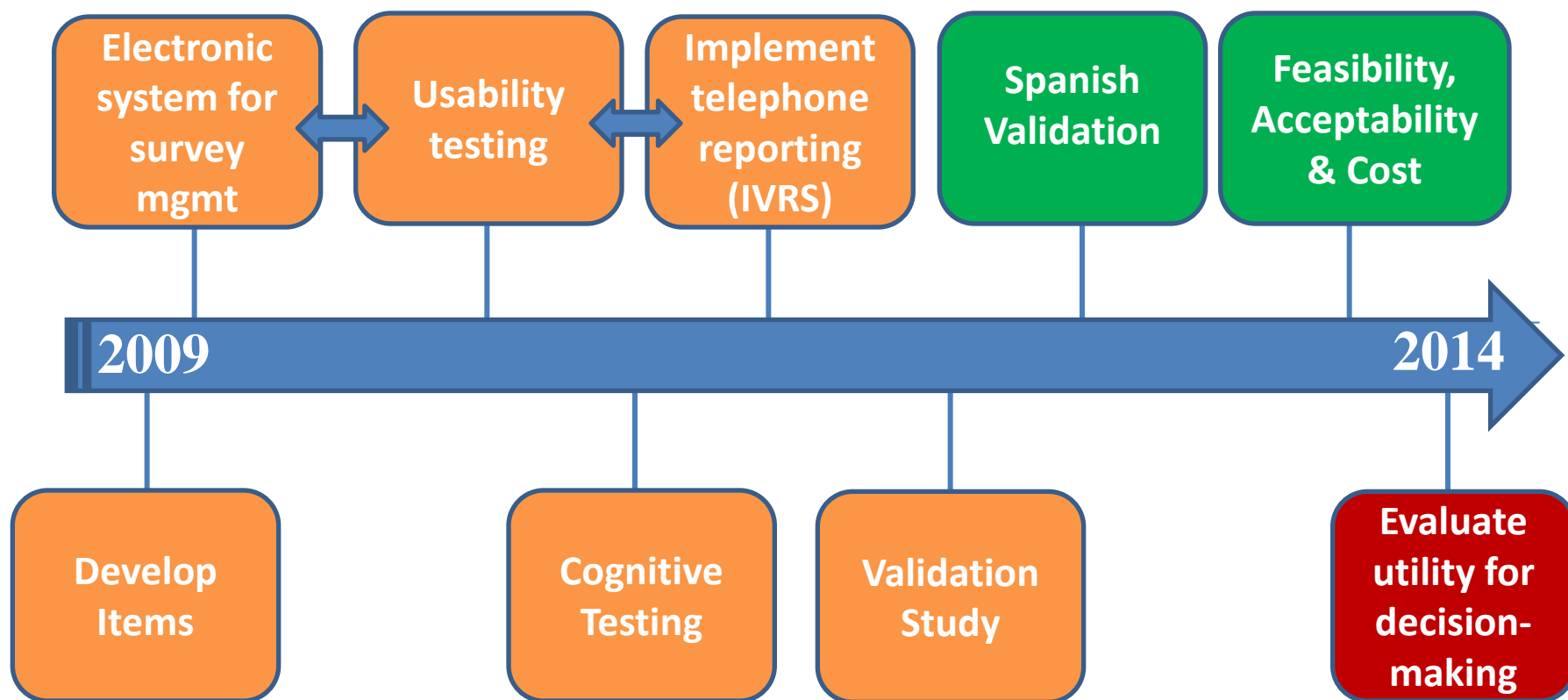
Cardio/Circulatory

- Swelling*
- Heart Palpitations

Visual Perceptual

- Blurred vision
- Flashing lights
- Visual floaters
- Watery eyes
- Ringing ear

- 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



PRO-CTCAE: Evidence for Reliability and Validity¹⁻³

- Studies conducted in diverse samples all of whom were receiving cancer-directed therapy;
- Samples enriched for lower educational attainment, racial/ethnic diversity, and lower performance status
 - Item development: rigorous process mapping out of the CTCAE and building phrasing from legacy PRO measures
 - Cognitive interviewing to establish content validity
 - Psychometric validation
 - Almost all items met one or more a priori criteria for validity
 - Majority of items distinguished subgroups based on PS, disease site, and/or treatment characteristics

¹Hay et al (2013). 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* July 20 2013 [Epub ahead of print]

²Dueck et al. Validity and reliability of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Manuscript in preparation for *Journal of Clinical Oncology*

³Basch et al. Development of the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Manuscript under review at JNCI.

System for Electronic Data Capture

English Español

Quickstart Guide Instructional Video

On-screen keyboard

Username

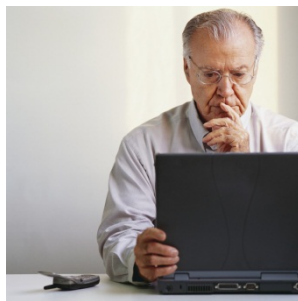
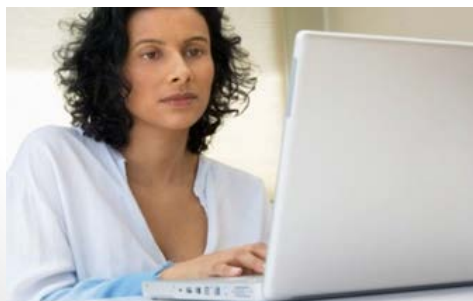
Password

Log in

[Forgot username?](#) [Forgot password?](#)

DISCLAIMER:

For patients using this system, the information you provide is for research purposes only. We will not give this information to the medical staff that treat you. **It is very important that you talk with your health care team about any symptoms that you have.**



E-Mail Notification

The screenshot shows a web browser window with the URL `qa.semanticbits.com/proctcae/pages/participant/participantInbox?lang=`. The page title is "PRO-CTCAE". A blue header bar contains "Welcome pt001" on the left and "Home" and "Log out" buttons on the right. Below the header, there is a navigation area with "English" and "Español" buttons, and an "Instructional Video" link with a play button icon.

The main content area is titled "Inbox(1)" and contains the text "You have [1] survey to fill out." Below this is an "Instructions" section: "Please see the list below for any survey(s) for you to fill out. Please click on the 'Start' button to begin a survey. Please complete the survey before it is due."

The "Available Surveys" section contains a table with the following data:

Name	Status	Due	
PRO-CTCAE Assessment for N1048 PROSPECT	Not started	in 2 days	Start

An orange arrow points to the "Start" button in the table. At the bottom left of the page, the text "version 2.1 20120925134329" is visible.

Conditional Branching

qa.semanticbits.com/proctcae/pages/form/submit?id=16654

Welcome pt001 [Home](#) [Log out](#)

Page: 1 of 16
Progress:

Please think back over **the past 7 days:**

What was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?

version 2.1 [20120925134329](#)

Conditional Branching

The screenshot shows a web browser window with the URL `qa.semanticbits.com/proctcae/pages/form/submit?id=16654`. The page title is "PRO-CTCAE". A blue header bar contains "Welcome pt001" on the left and "Home" and "Log out" buttons on the right. Below the header, the text "Please think back over **the past 7 days:**" is displayed. To the right of this text is a progress indicator showing "Page: 1 of 16" and "Progress:" with a small blue bar. The main question is "What was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?". Below the question are five buttons: "None" (highlighted in green), "Mild", "Moderate", "Severe", and "Very severe". A large green arrow button labeled "Next" is centered below the buttons. In the bottom left corner, the text "version 2.1 20120925134329" is visible.

qa.semanticbits.com/proctcae/pages/form/submit?id=16654

PRO-CTCAE

Welcome pt001

Home Log out

Please think back over **the past 7 days:** Page: 1 of 16 Progress:

What was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?

None Mild Moderate Severe Very severe


Next

version 2.1 20120925134329

Conditional Branching

qa.semanticbits.com/proctcae/pages/form/submit?id=16654

Welcome pt001 [Home](#) [Log out](#)

Page: 1 of 16
Progress: 

Please think back over **the past 7 days:**

What was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?

How much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?

Write Ins for Additional Symptoms

The image shows a web browser window with the URL `qa.semanticbits.com/proctcae/pages/form/addMorequestion?p=16`. The page title is "PRO-CTCAE". A search input field contains the text "Back". To the right of the input are "Add" and "Clear" buttons. A dropdown menu is open, listing the following symptoms: "Back ache", "Back distress", "Back pain", "Back pain (with radiation)", "Back pain (without radiation)", and "Back pain aggravated". The "Back ache" option is highlighted in blue. Below the dropdown is a large green "Next" button. At the bottom of the screen, a virtual keyboard is visible, with the "Back" key highlighted. Two orange arrows point to the search input and the "Back ache" option in the dropdown.



PRO-CTCAE Implementation

Use in 2 cooperative group trials

- Feasibility and acceptability
- Data quality
- Resource requirements and cost
- Measurement characteristics/interpretability:
 - Responsiveness to change
 - Sensitivity to detect differences between treatment groups

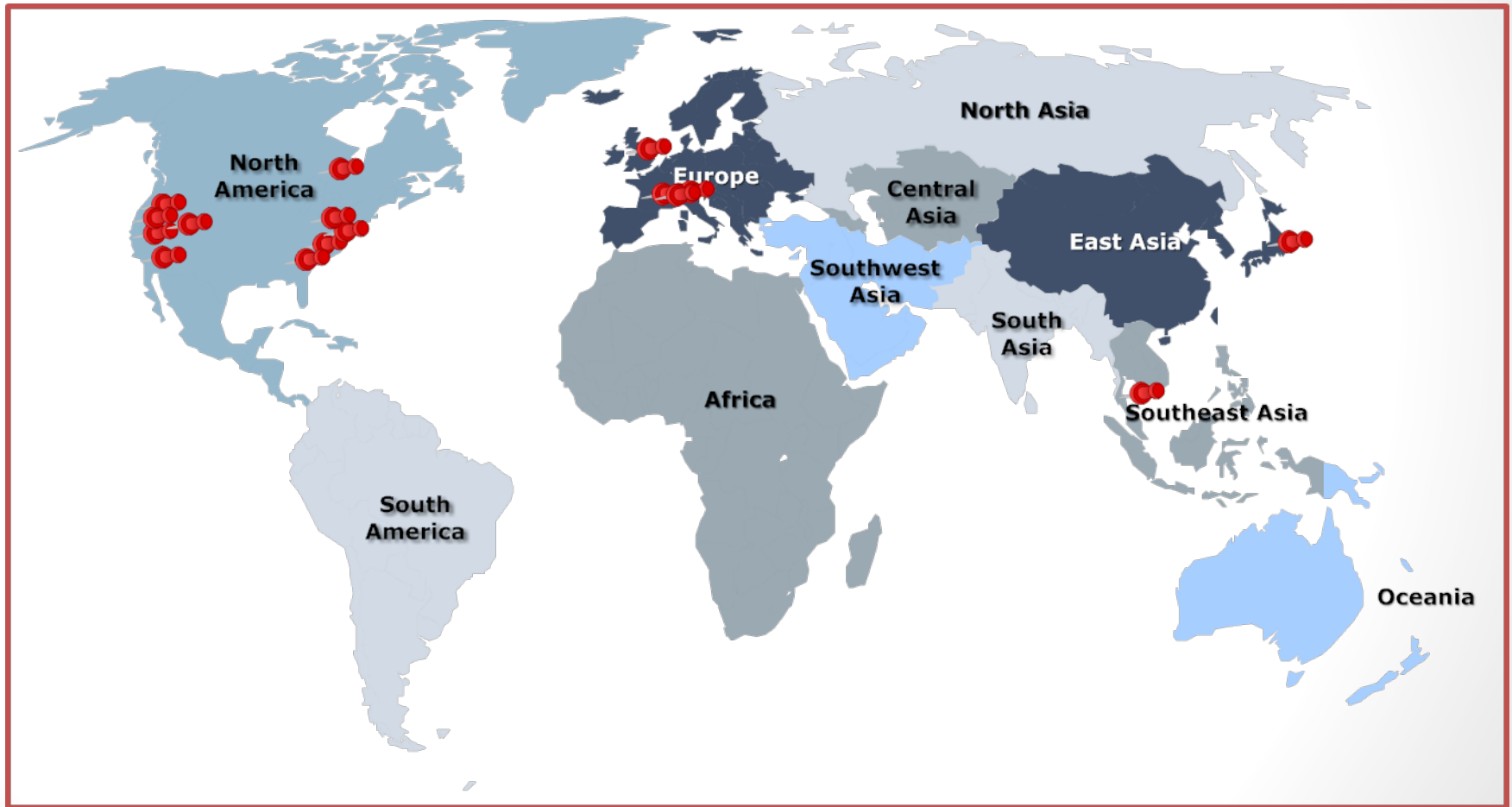
RTOG 1012: Phase II Randomized Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis-Related Pain During the Treatment of Lung Cancer

NCCTG 1048: A Phase II/III trial of Neoadjuvant FOLFOX, with Selective Use of Combined Modality Chemoradiation versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision

Early Adopters

- 35 Early adopters in academic settings and in industry are testing PRO-CTCAE in trials and observational studies
- Collaboration agreements (35) established with these investigators:
 - Stimulate efficient and coordinated testing of PRO-CTCAE in clinical trials
 - Allow for sharing of data and collaborative analysis
 - Generate evidence about best approaches for particular study contexts and patient populations

Collaboration Agreements Established with Investigators in 8 Countries





Where Are We Heading Next?

- Standard analytic validation for a patient-reported outcome measure completed
- PRO-CTCAE can be used for descriptive information
- Understanding of clinical validity, interpretation, and clinical utility is evolving

Key Issues

- Identify trial contexts and investigational therapies where PRO-CTCAE will be particularly useful
- Interpret PRO-CTCAE scores to assign a grade
- Delineate principles for design and interpretation of trials that incorporate patient self-reporting of adverse effects and yield interpretable and meaningful information



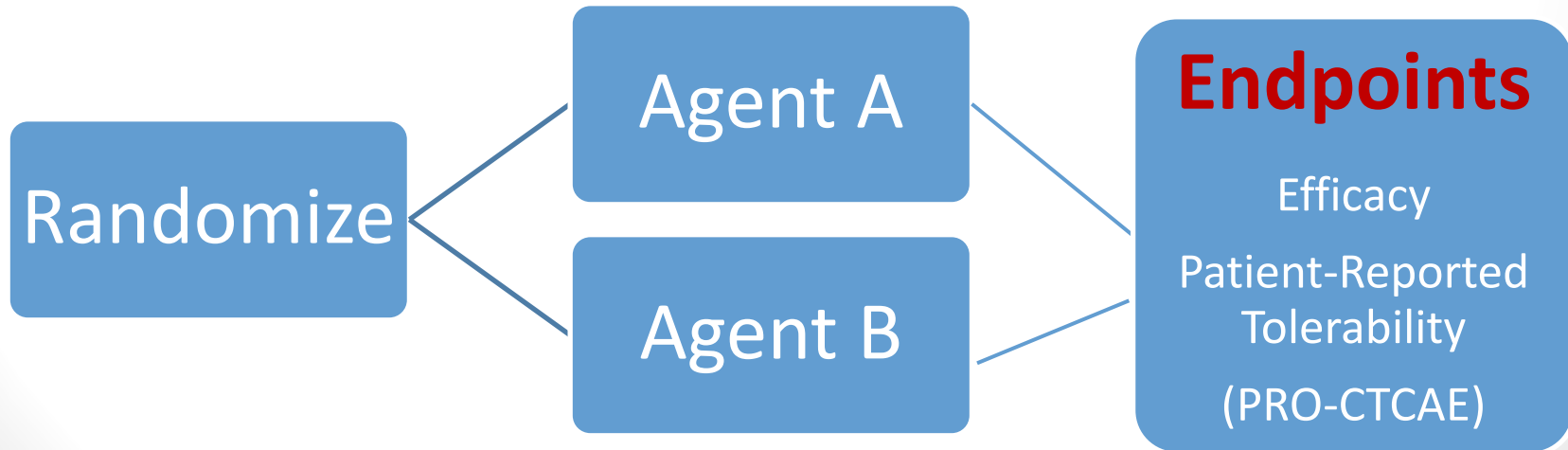


Utility of PRO-CTCAE

- **Phase I: Exploratory**
 - Gauge side effects relative to dose escalation; refine measurement approaches (items, timing) for later phase studies
- **Phase II: Describe Toxicity in Depth**
 - Assess tolerability of the recommended phase II dosing
 - Identify chronic symptomatic toxicities that may impair adherence
 - Explore approaches (schedule/dosing, supportive care) to reduce symptomatic adverse effects
- **Phase III: Assess Overall Benefit/Risk for Regimen**
 - Evaluate efficacy and tolerability on a wider scale
 - Assess impact of dosing modifications to reduce chronic symptomatic toxicities on overall benefit/risk
- **Phase IV: Efficacy → Effectiveness**
 - Optimize tolerability
 - Tailor regimens for vulnerable sub-populations (comorbidities, frail, older adults)

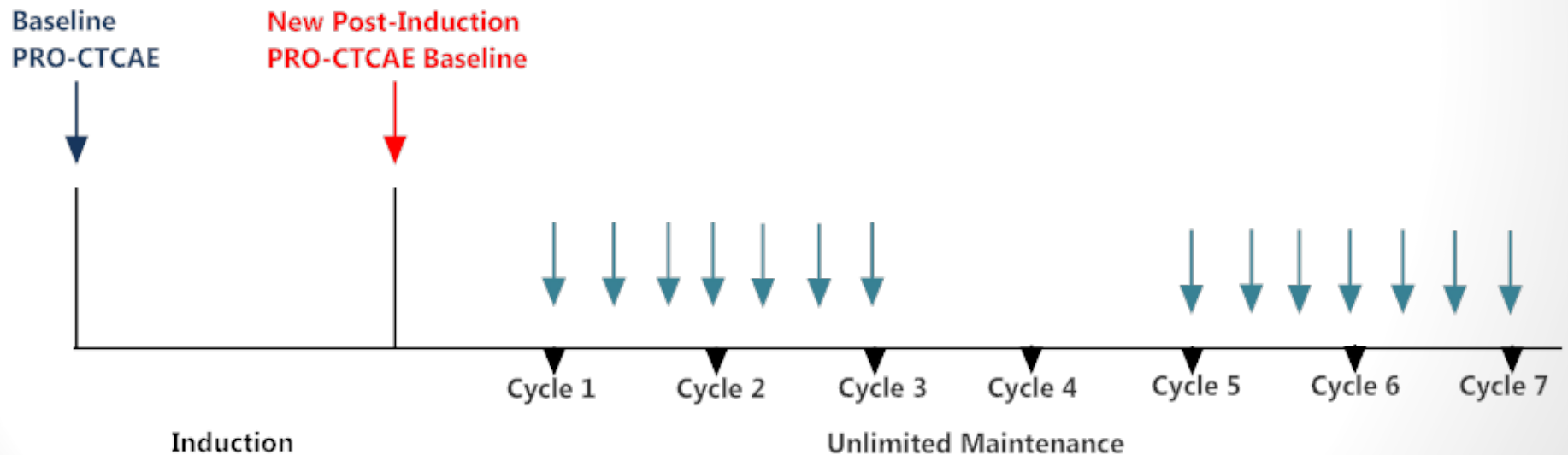
Phase 2 B Comparative Tolerability

- Two oral agents with comparable efficacy and clinician-rated toxicity in Phase II trials
 - Research Question: Are there subtle tolerability differences between the two agents that might become important in Phase III and which can be detected with inclusion of PROs in Phase II?
- Randomized phase II B study with efficacy and patient-reported tolerability as the primary endpoints



Tolerability of Maintenance Therapy

Research Question: What is the chronic tolerability of unlimited bortezomib maintenance therapy in multiple myeloma in remission after induction?





Scaling Towards Implementation

- **Increase accessibility for pediatrics**
- **Incorporate into CTCAE**
 - Demonstrate clinical validity/interpretability and utility across trial designs and populations so that integration into CTCAE is empirically-driven
- **Ongoing efforts to embed PRO-CTCAE into existing clinical trials**
 - Understand how reporting could influence dose modifications
 - Efficiently incorporate into trial design to yield information that is interpretable and useful for decision-making (individual and trial-level)
- **Integrate PRO-CTCAE into Medidata Rave (NCI's Remote Data Capture System)**



Discussion with CTAC Members

- What are the trial populations, study designs, and therapeutic contexts in which PRO-CTCAE will be particularly useful?
- As key stakeholders in NCI 's clinical trials system, we need in your engagement and perspectives about:
 - Consensus-based and data-driven approaches to mapping PRO-CTCAE responses into CTCAE grading
 - Best practices for aggregate reporting of PRO-CTCAE outcomes
 - Best practices for integration of PRO tolerability data into real-time monitoring and analysis/interpretation of trial level outcomes

Appendices: Supplementary Material

Appendix A:

Cognitive Interviewing Study

- Aim: Evaluate comprehension/interpretation of PRO-CTCAE terminologies and response options
- Methods: 3 rounds of cognitive interviews
- Sample: 127 patients with advanced cancer receiving active treatment at 4 cancer centers
 - 35% <high school; 28% non-white; 59% female
- Results:
 - 63/80 symptom terms generated no cognitive difficulties
 - 17 terms (e.g. diarrhea, insomnia, wheezing) modified and retested with no further difficulties
 - Distinction among frequency, severity, and interference understood



Appendix B:

Validation Study Aims and Methods

Aim: Examine validity and reliability

Methods:

- Convergent validity: associations with EORTC QLQ C30 scores
- Known-groups validity: groups based on disease site, clinical characteristics, and ECOG PS
- Test-retest reliability: assessed on consecutive days in a subsample

Sample: 975 patients who had received cancer-directed therapy in the prior two weeks

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

Appendix B:

Validation Study Results

- **PRO-CTCAE demonstrates favorable validity and reliability in a large, heterogeneous sample of patients undergoing cancer treatment**
 - Most PRO-CTCAE items (116/124) were shown to be valid across one or more validity criteria ($p < .05$)
 - 8 items (rare events with low endorsement) could not be meaningfully validated in this sample
 - All PRO-CTCAE items correlated with EORTC QLQ-C30
 - 96/124 PRO-CTCAE items distinguished subgroups based on PS, disease site, and/or treatment characteristics
 - Acceptable test-retest reliability across tested items (Median ICC 0.77)

Appendix C:

Ongoing Validation Analyses

- **Mode equivalence**
 - Comparison of paper, web, and telephone administration on the same day
- **Recall Period**
 - Comparison of 28 daily ratings to 1-, 2-, 3-, and 4-week recalled ratings
- **Interpretability**
 - Relationships among symptom attributes (frequency, interference, severity)
 - Cut scores