National Cancer Institute

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

PRO-CTCAE

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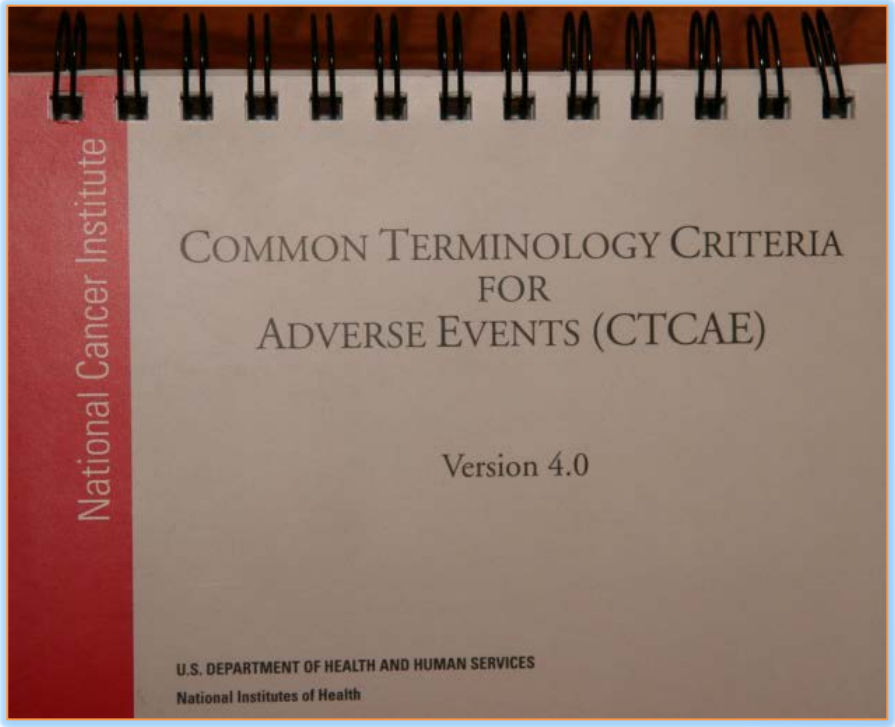
PRO-CTCAE

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

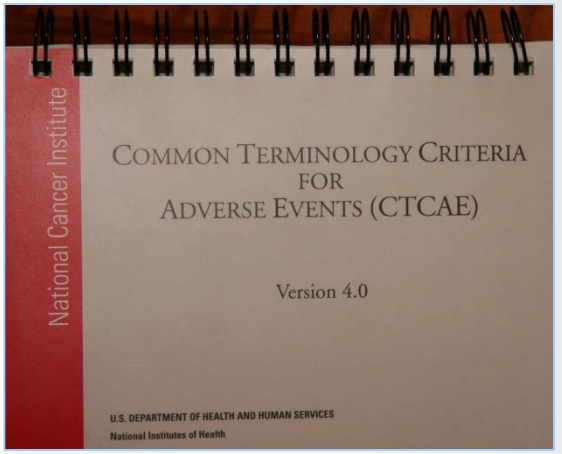
- Treatment-related toxicity (safety and tolerability)
  - Fundamental outcome when drawing conclusions about therapeutic effectiveness, including comparative effectiveness
  - Currently evaluated by clinicians using **C**ommon **T**erminology **C**riteria for **A**dverse **E**vents (***CTCAE***)

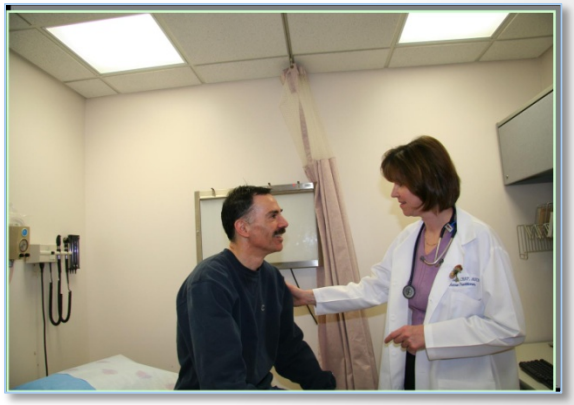


PRO-CTCAE

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

- 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 clinicians[1]
  - 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 trialists[2]





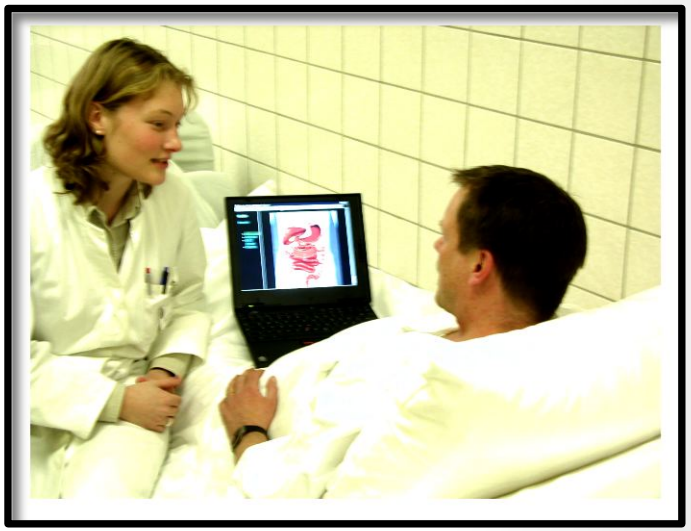
[1]Xiao et al. (2013). Comparison between patient-reported and clinician-observed symptoms in oncology. *Cancer Nurs.*,36(6):E1-E16

[2]Bruner 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

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

- **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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- We gratefully acknowledge our study participants and patient representatives!

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





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

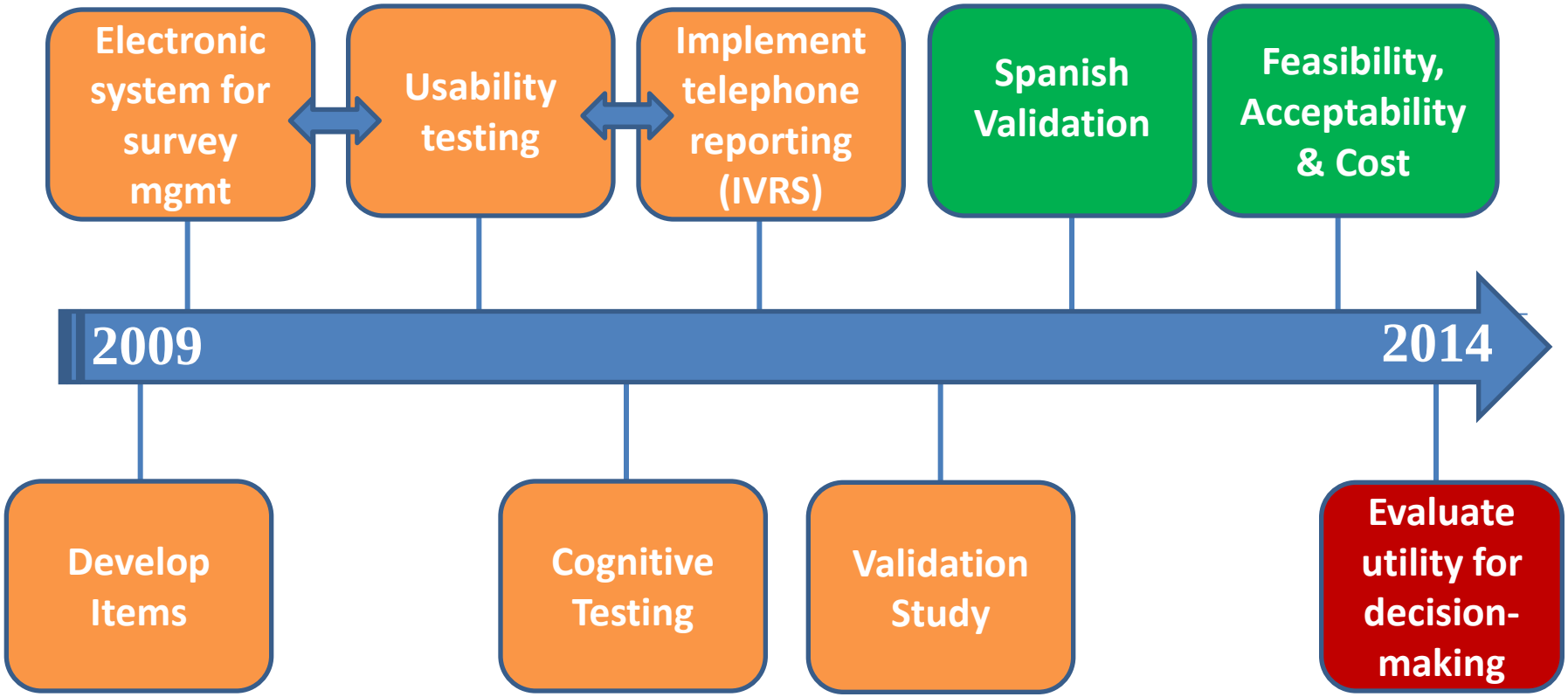
Gastro-Intestinal
- Taste Changes*
- Decreased appetite*
- Nausea*
- Vomiting*
- Heartburn
- Gas
- Bloating
- Hiccups
- Constipation*
- Diarrhea*
- Abdominal pain
- Fecal Incontinence

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 Validity[1-3]

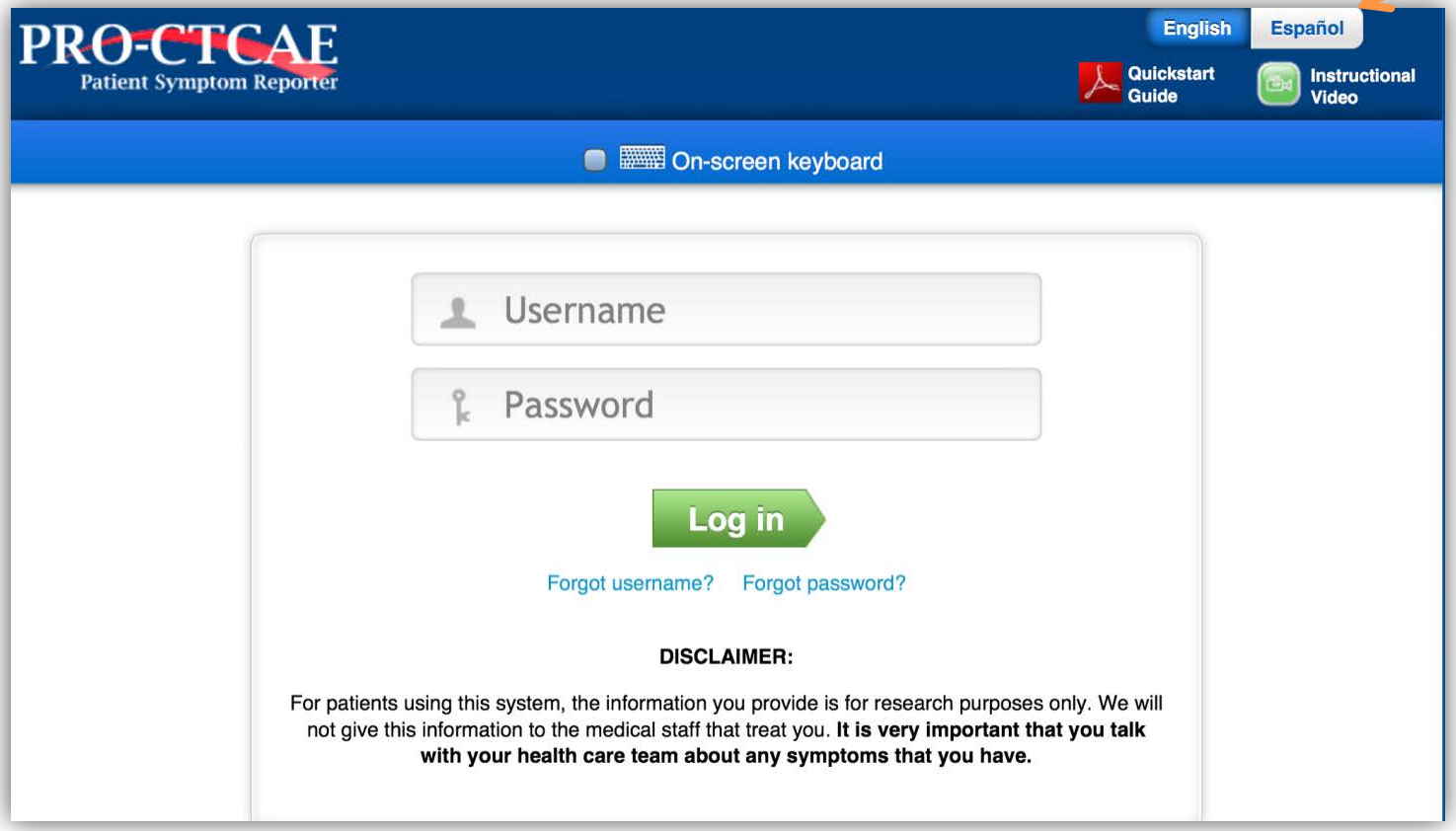
- Studies conducted in diverse samples all of whom were receiving cancer-directed therapy;
- Samples enriched for lower educational attainment, racial/ethnic diversity, and lower performance status
  - Item development: rigorous process mapping out of the CTCAE and building phrasing from legacy PRO measures
  - 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

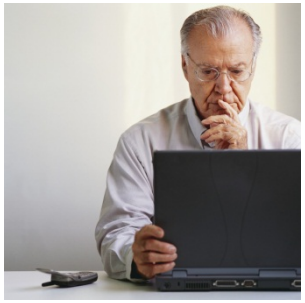
[1]*Hay et al (2013).* Cognitive interviewing of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) to support content validity. *Quality of Life Research July 20 2013 [Epub ahead of print]*

[2]*Dueck 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

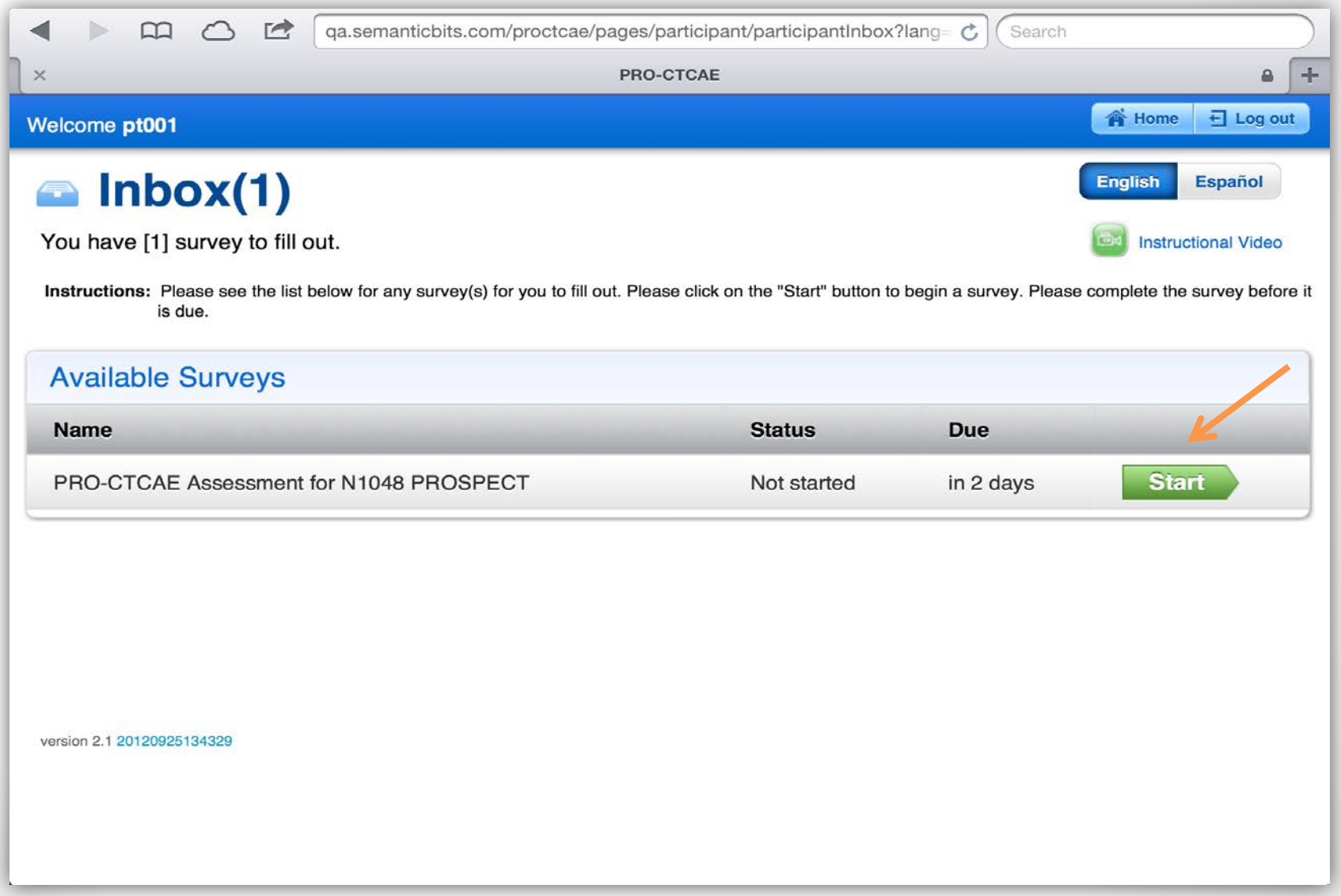
[3]*Basch et al.* Development of the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Manuscript under review at JNCI.

System for Electronic Data Capture

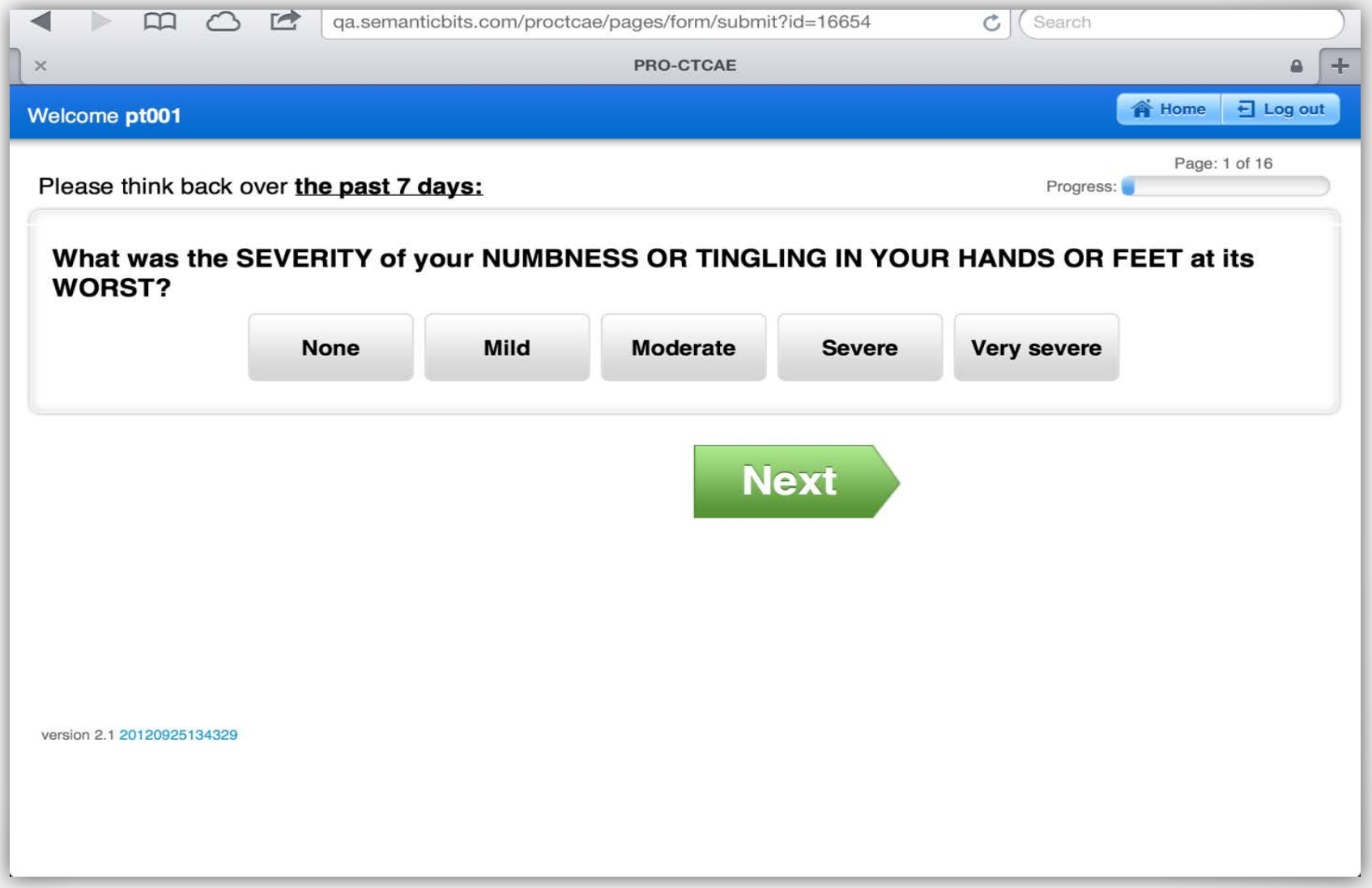




E-Mail Notification



Conditional Branching



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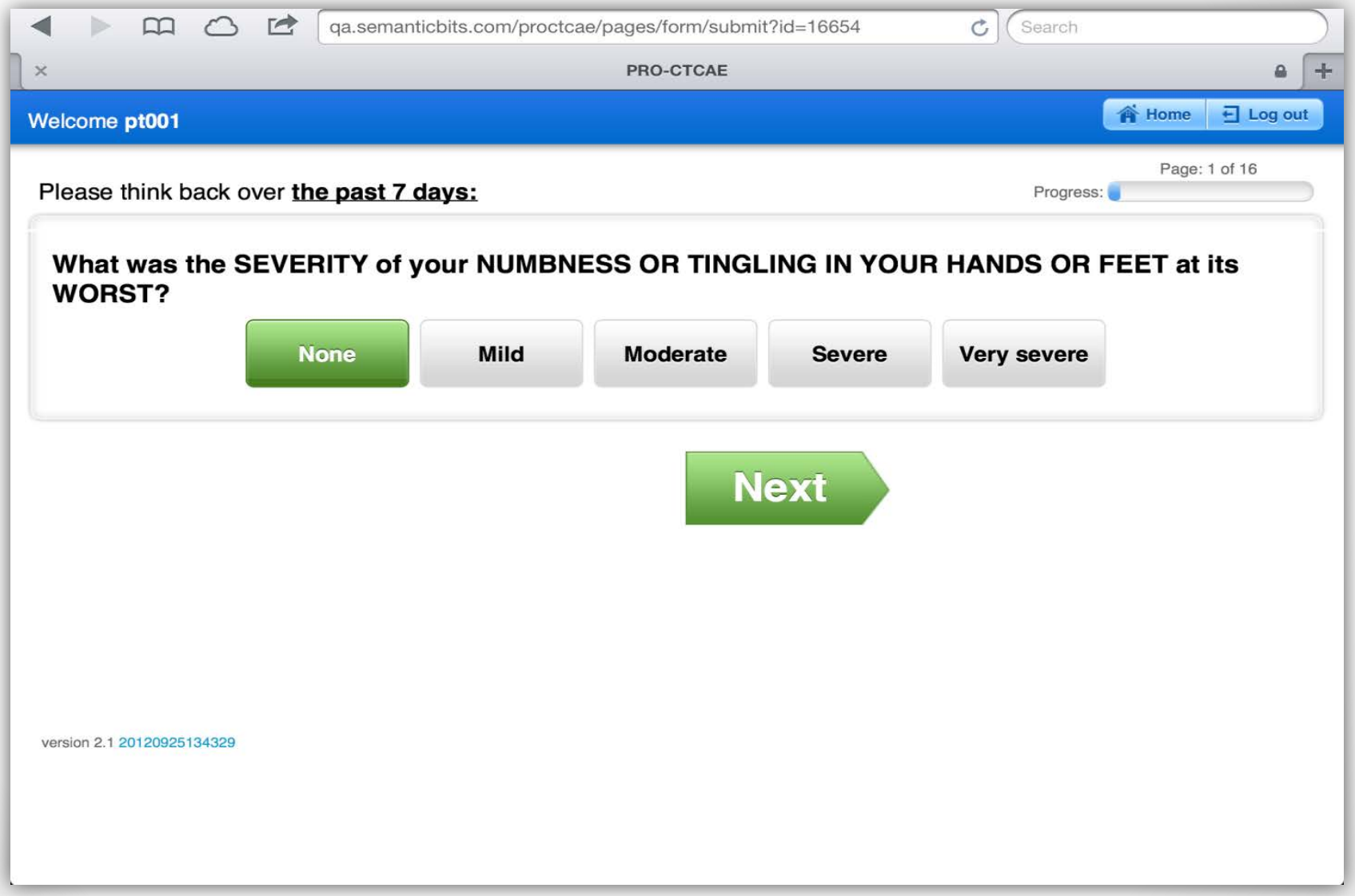

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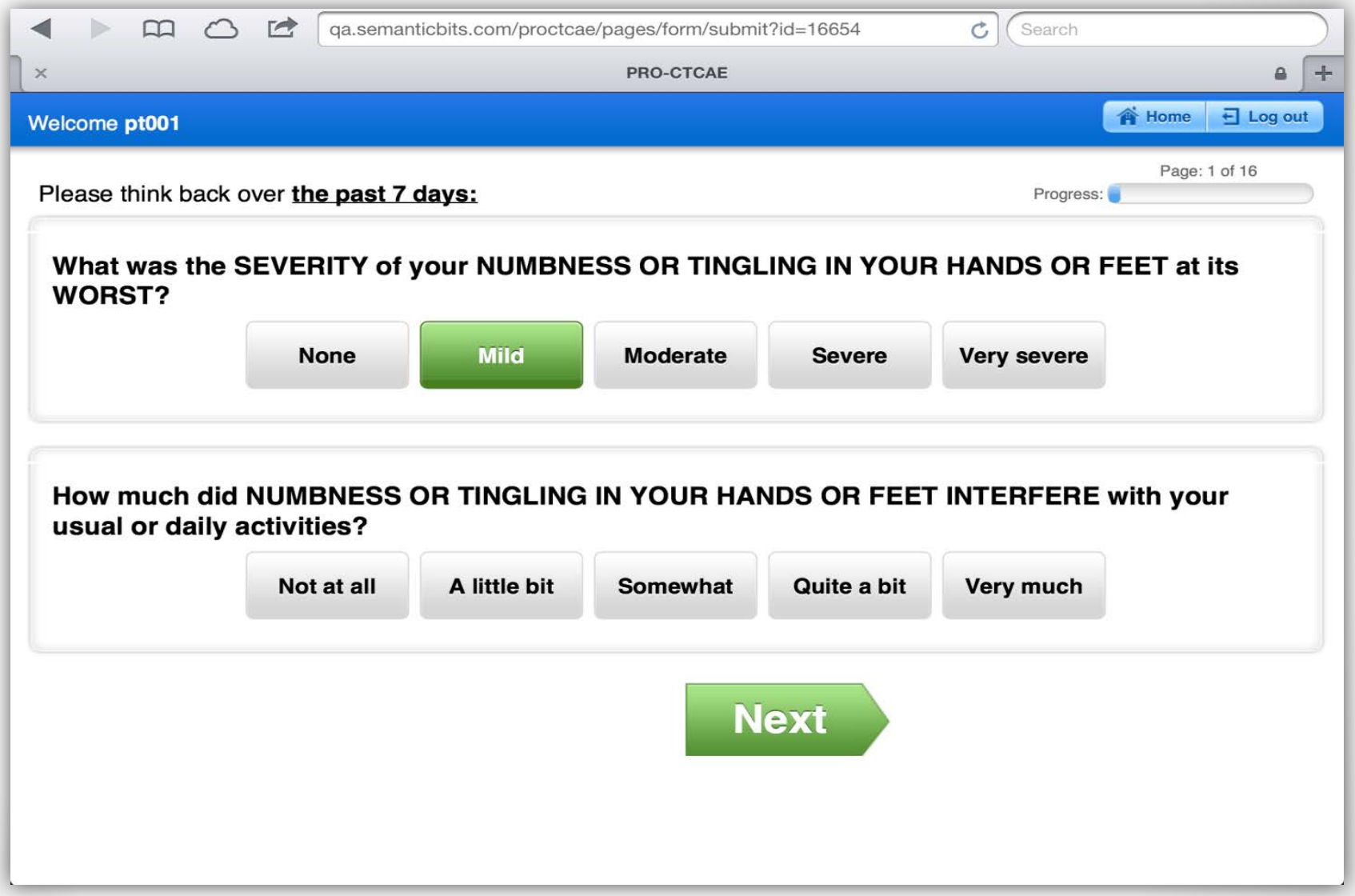
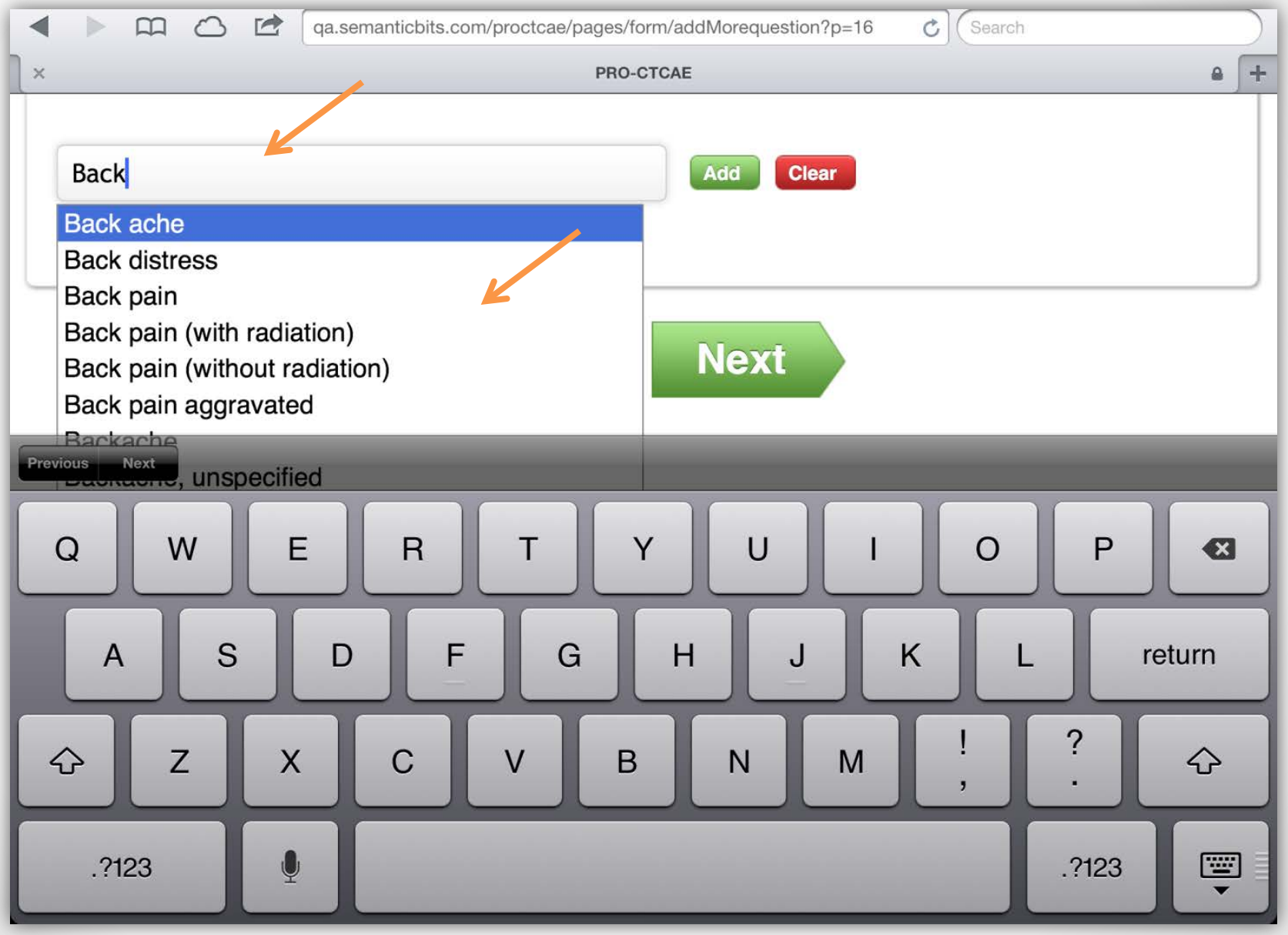


Write Ins for Additional Symptoms



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

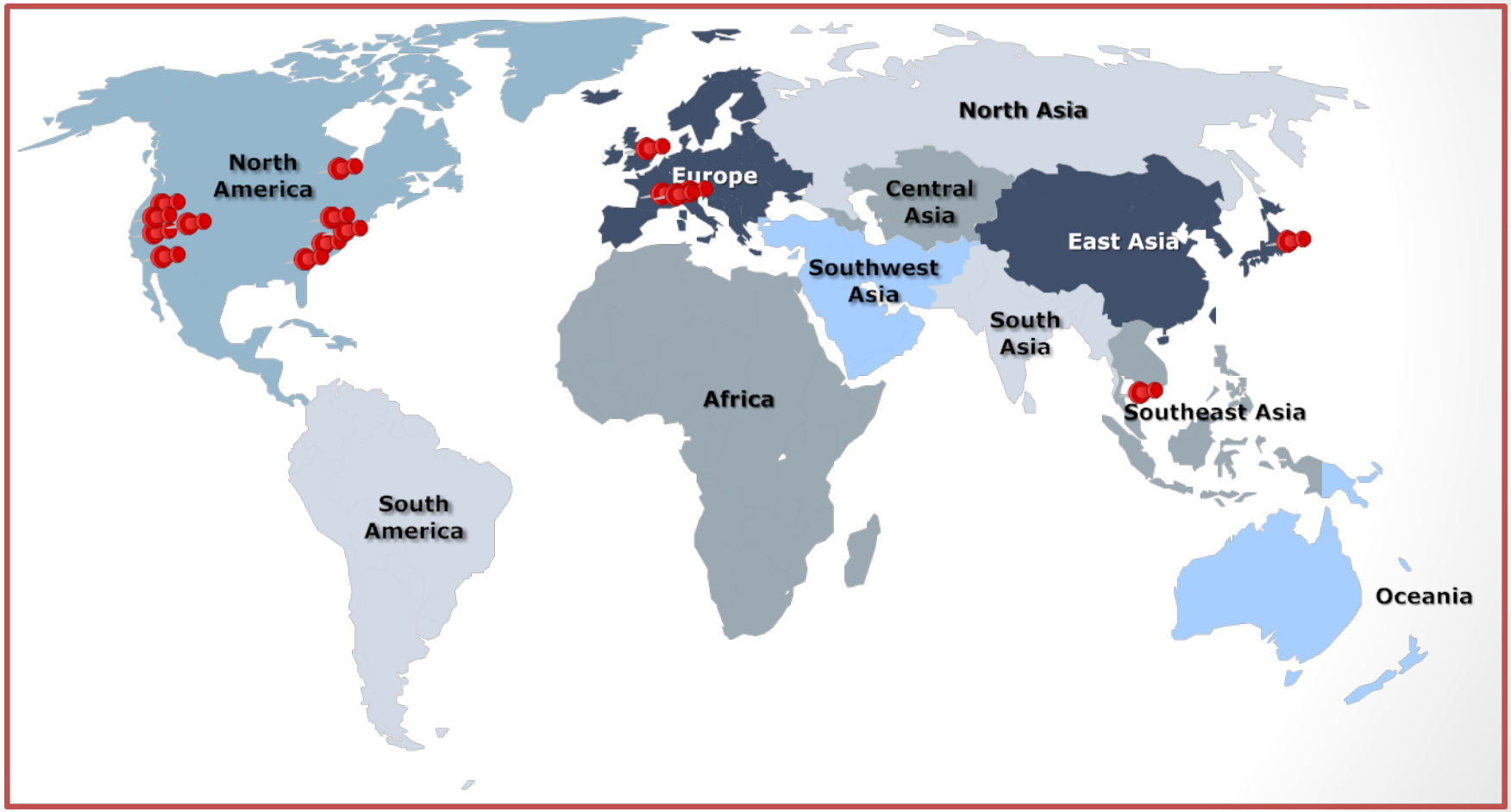
RTOG 1012: Phase II Randomized Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis-Related Pain During the Treatment of Lung Cancer

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

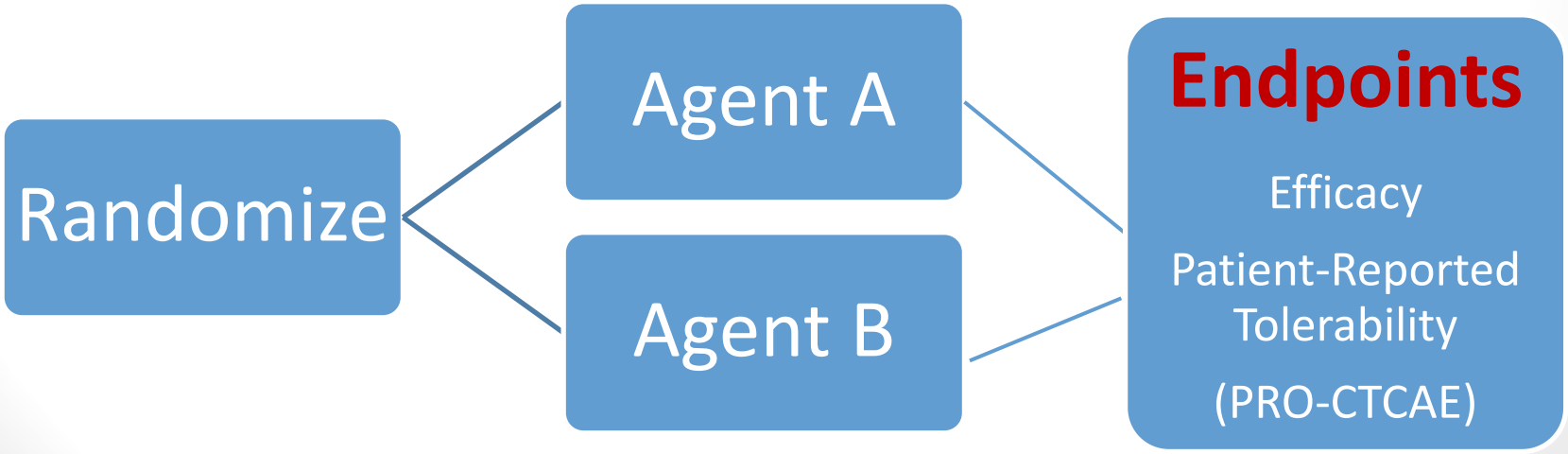
- Identify trial contexts and investigational therapies where PRO-CTCAE will be particularly useful
- Interpret PRO-CTCAE scores to assign a grade
- Delineate principles for design and interpretation of trials that incorporate patient self-reporting of adverse effects and yield interpretable and meaningful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

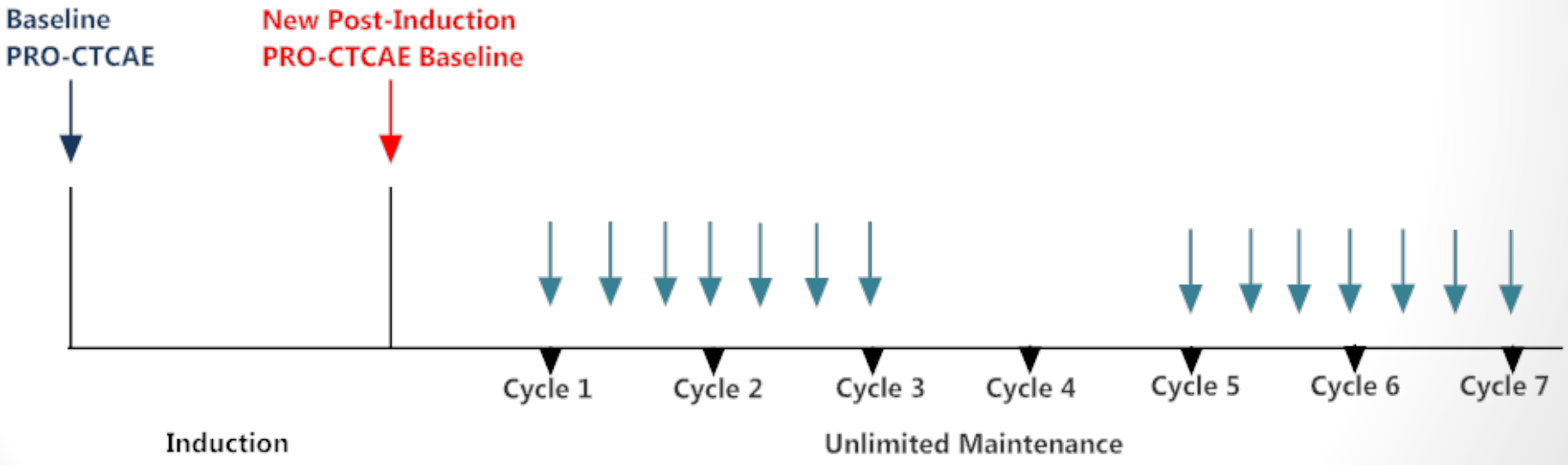
Phase 2 B Comparative Tolerability

- 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

Hay et al (2013) . Quality of Life Research July 20 2013 [Epub ahead of print]

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)

Dueck et al. Manuscript in preparation for JNCI

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