Patient-Centered Endpoints in Oncology

SIXTH ANNUAL

PATIENT-REPORTED OUTCOME CONSORTIUM WORKSHOP

April 29 - 30, 2015 ■ Silver Spring, MD

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Session Objectives

Historically, few label claims have been granted in oncology. In the past years, FDA and pharma have increased the attention for PRO in oncology. This session focuses on how patients' perspective is best captured in clinical trials in this new environment and what to measure.

Session Participants

Moderator

- Katarina Halling, MSc – Patient-Reported Outcome (PRO) Group Director, AstraZeneca and Industry Co-Director, PRO Consortium

Presenters

- Cindy Geoghegan - Principal, Patient and Partners LLC
- Paul G. Kluetz, MD - Office of Hematology and Oncology Products, FDA
- Ethan Basch, MD, MSc - Cancer Outcomes Research Program, University of North Carolina

Patient-centricity in oncology

There a many ways pharma can incorporate patients' voice in drug development and engage with patients

- Patient interviews as foundation for efficacy and safety endpoints
- Risk benefit patient interviews
- Social media
- PRO CTCAE
- Patient-friendly summaries of interviews

What is critical now?

Pharma perspective

- New innovative approaches incorporated into drug development process
  - New endpoint development
  - Optimising the existing ones
- Open dialogue between stakeholders
- Scalability of new approaches
  - We need methods and endpoints that can be included in large multinational clinical trials with accelerated speed

Cindy Geoghegan
Principal, Patient and Partners LLC

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Optimization and Standardization of PRO in Cancer Clinical Trials

Paul Kluetz, MD
Office of Hematology and Oncology Products
U.S. FDA

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Feedback from the PRO community: To sum it up… Frustration

- FDA provides inconsistent advice from review divisions and from SEALD
- PRO Guidance is Infeasible – Instrument development has suffered
- FDA Oncology Labels contain less PRO data than other Therapeutic Areas and Europe

Challenges for PRO in Oncology

- Lack of agreed upon instruments (questionnaires)
- Trial designs not optimized for PRO
- Significant portion of PRO data frequently missing
- Lack of standardization in data analysis
- Lack of standardization in data presentation
- Lack of familiarity with PRO data analysis for Oncology clinical trial reviewers (both statistical and clinical) as we have relied on survival and radiographic evidence of treatment benefit

What FDA has Done…

Goal: Detailed, consistent and proactive PRO advice

- Increased OHOP-SEALD Collaboration
  - Monthly Working Group, Collaborative Meetings
- Improved Clinical Reviewer PRO Expertise
  - Divisional PRO leads
  - Divisional Associate Director for Labeling
- Educational Opportunities for clinical reviewers
  - Monthly OHOP PRO Case Series and other Educational Outreach

2009 PRO Guidance

- Framework for optimal instrument development and trial design to support PRO labeling claims
- FDA acknowledges the rigor of this guidance
- We do not wish to abandon a “very good” PRO strategy for the sake of “the perfect”.
- However; there is much we can do to improve PRO instrument optimization, trial conduct and data analysis in Oncology trials.

Instrument Development

- **Long Term**: Encourage New Instrument Development
- **Short Term**: Identify existing instruments that can be used or modified as "reasonable" for use in trials
  - FDA Compendium of Clinical Outcome Assessments announced 4/1/2015
- Optimal choices for instruments will be an iterative process
- OHOP acknowledges that the PRO guidance is a roadmap for "gold standard" PRO instruments, but that flexibility may need to be exerted.

FDA has focused on adequacy of instruments

There is realization that there is MUCH we can do NOW to improve trial design, data capture, data analysis and presentation

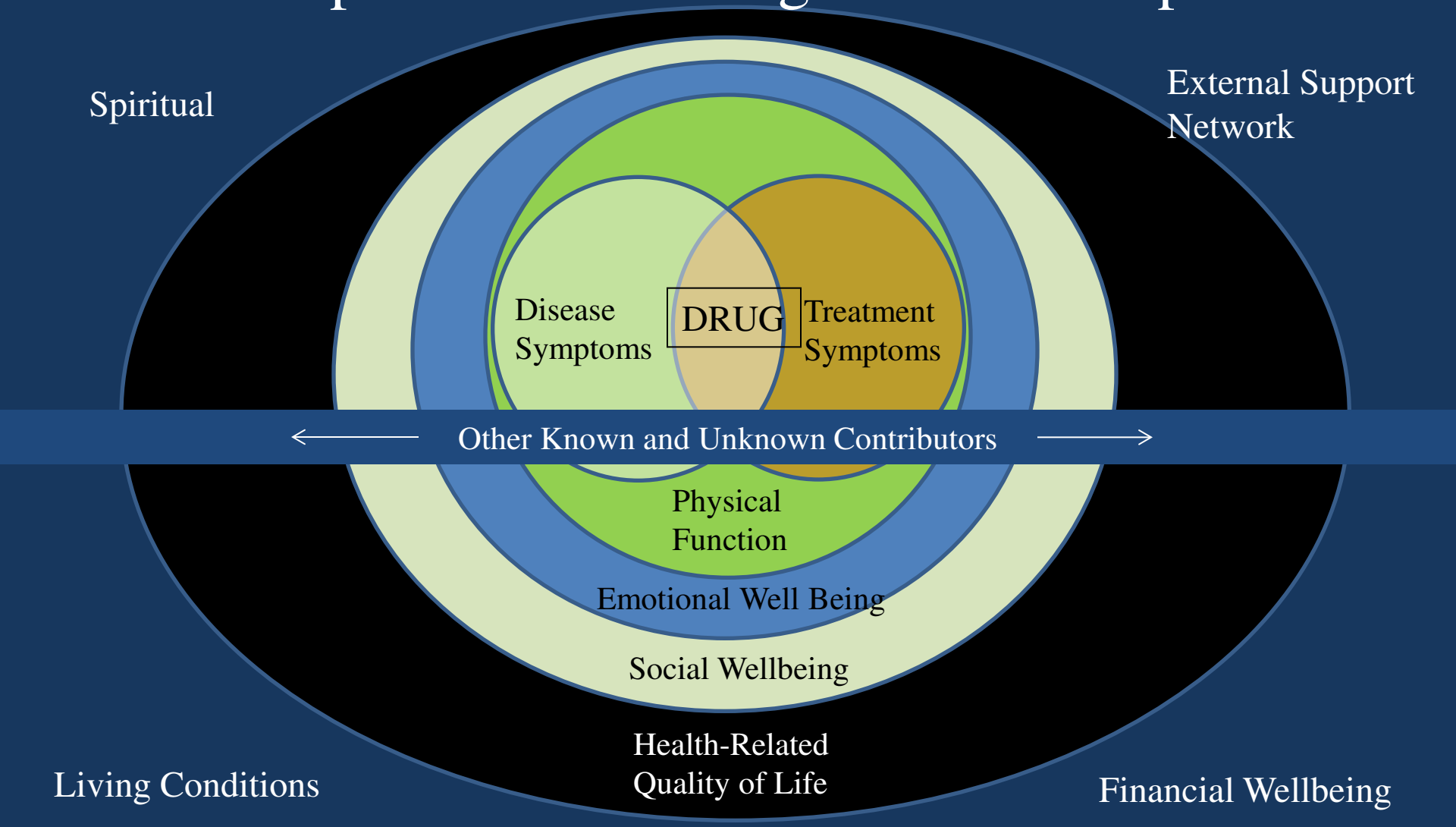
Clinical Trial Realities-
We must Pick our Battles

- We cannot capture and measure everything we would like in a clinical trial setting

- This is particularly important when considering PRO as there is some degree of burden in filling out questions and collecting and handling all that data

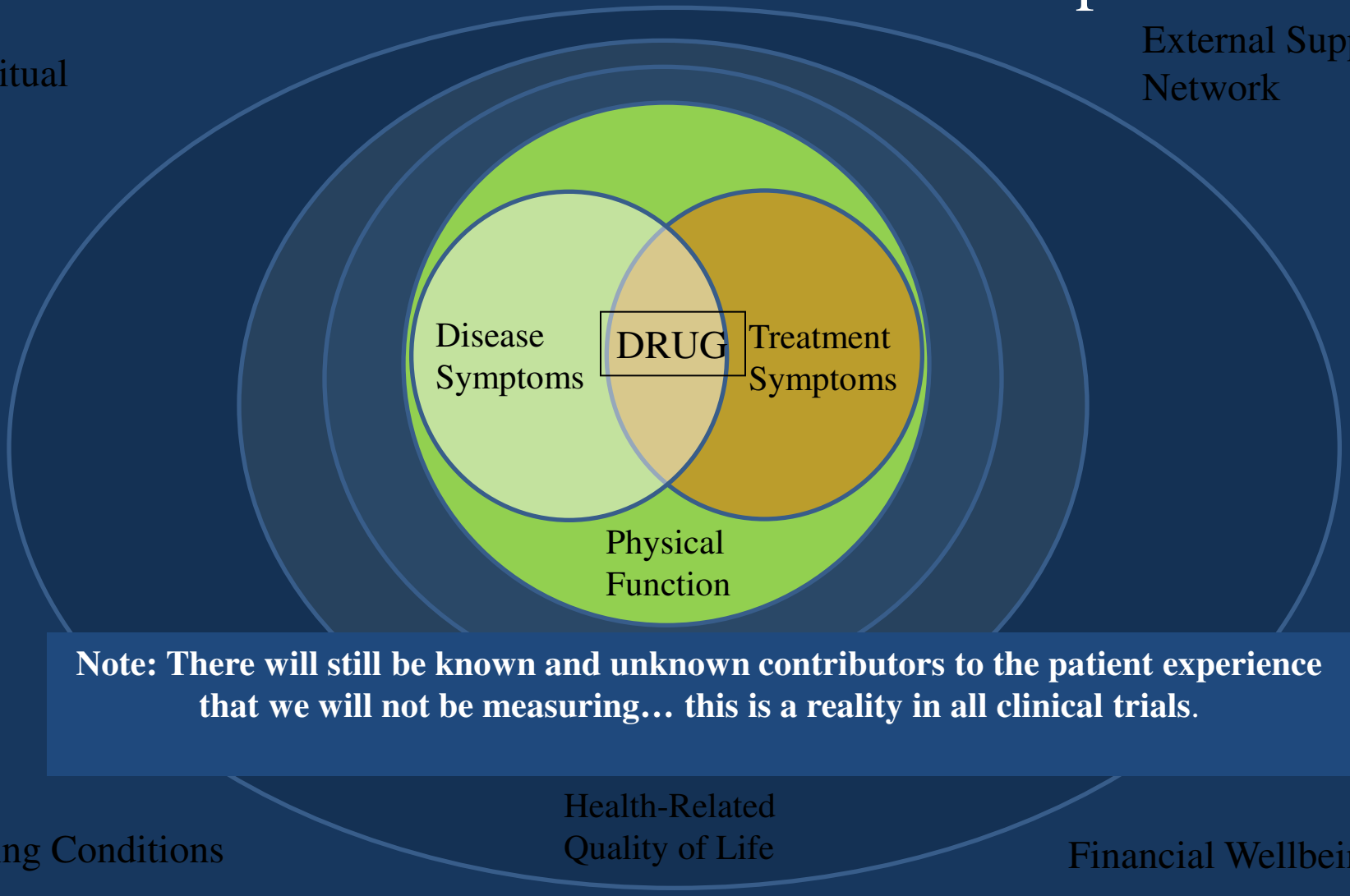
- We MUST **OPTIMIZE and STANDARDIZE** PRO in Cancer Clinical Trials

Could we better define core PRO concepts that are most proximal to a drug's effect on a patient?



"Quality of Life"

And improve accuracy and sensitivity of measurement of these core concepts?



Note: There will still be known and unknown contributors to the patient experience that we will not be measuring… this is a reality in all clinical trials.

Core Concepts: Disease Related Symptoms, Treatment Related Symptoms, Physical Function

- **Disease Related Symptoms:**
  - Heterogeneous cancer contexts will require a range of different instruments
  - Can we repurpose existing instruments while we encourage optimal development of new instruments?

- **Physical Function:**
  - Physical Function Status agnostic to disease and therapy
    - A single measure for all cancer clinical trials would greatly improve standardization
  - Short Term: Physical function domain of an existing HrQOL instrument such as the QLQ-C30?
  - Short to Long Term: PROMIS appears well-suited to measure this concept

Core Concepts: Disease Related Symptoms, Treatment Related Symptoms, Physical Function

- Treatment related adverse events (AEs) are very familiar to oncologists, statisticians and clinical trialists
  - ClinRo: Common Toxicity Criteria of Adverse Events (CTCAE)
    - CTCAE adverse events are reported as descriptive data in all oncology FDA labels as incidence tables
  - PRO: Some existing HrQOL instruments include static AEs (neuropathy, nausea, etc.).
    - PRO-CTCAE developed as a PRO CTCAE library that can adapt to different classes of therapies being tested.
- The Office of Hematology and Oncology Products supports PRO-CTCAE as complimentary to labeled ClinRo AEs
  - Provided data are captured adequately, PRO-CTCAE could be included in FDA label descriptively, alongside ClinRO CTCAE data
  - We are proactively giving this advice to sponsors of oncology clinical trials

Ideally, PRO Labeling would provide strong data on all 3 core concepts

- **Efficacy: Does the drug provide superior improvement in disease related symptoms or functional deficits?**
  - Disease Related Symptom Score appropriate for the context
    - (Pain, Total Symptom Score, Performance related outcomes)
    - More conducive to formal statistical analysis (statistical superiority)

- **Patient Experience: How do patients feel while on therapy?**
  - Adverse events from therapy (PRO-CTCAE)
  - Physical function / Performance status (PROMIS? Domain of Existing Instrument?)

- As we optimize and standardize PRO, we expect more PRO data will be labelled.

- PRO data, whether labeled or unlabeled, will be integrated into the risk:benefit

There is Cause for Optimism…

- New drugs are showing unprecedented efficacy using objective efficacy endpoints (survival and radiographic endpoints)
- The full risk:benefit of these products would be augmented by accurate presentation of the patient experience
- We are increasingly seeing more thought put into PRO measures for registration trials, but we can all do more
- There is renewed effort and collaboration between the FDA and cancer drug development stakeholders to optimize and standardize the path to accurate, well-collected PRO data in FDA labels

PROs in Cancer Drug Development

Ethan Basch, MD MSc
University of North Carolina

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Rationale

- Cancer-related symptoms are common
- Cancer drugs often cause symptomatic toxicities
  - Affect tolerability, compliance, clinical outcomes
- Therefore essential to understand how people feel and function with oncology drugs
- Lack of understanding this = incomplete understanding of properties of drug
  - Inability to adequately balance benefit with risk
  - Danger of inappropriate dose/schedule
  - Lost opportunity for supportive measures
  - Inadequate information for prescribers and patients

Key Domains

1. Physical functioning
2. Disease-related symptoms
3. Symptomatic toxicities (treatment-related AEs)
4. Global HRQL/health state → QALYs

Symptomatic Toxicities (AEs)

1. About half of adverse reactions reported in cancer labels are symptoms
2. Currently rely on investigators to capture
   - Reliability low to medium
   - Under-grade and over-grade
3. Patients willing and able to self-report AEs

   >90% adherence with weekly web or IVR
4. Sharing patient-reported AEs with investigators
   - Investigators agree with patients; value input; take actions

Patient: P081091, Demo

Survey date: 6/15/2011 10:55 AM

Adverse symptom	Patient self report	Date	Agree?	Clinician reassign	Attribution
ALOPECIA	GRADE 0	6/15/2011 10:54 AM	Agree	GRADE 0	N/A
ANOREXIA	GRADE 1	6/15/2011 10:53 AM	Disagree	GRADE 2	Unrelated
COUGH	GRADE 1	6/15/2011 10:53 AM	Agree	GRADE 1	N/A
DYSPNEA	GRADE 1	6/15/2011 10:51 AM	Disagree	GRADE 2	Unlikely
EPIPHORA	GRADE 0	6/15/2011 10:55 AM	Agree	GRADE 0	N/A
EPISTAXIS	GRADE 0	6/15/2011 10:55 AM	Agree	GRADE 0	N/A
FATIGUE	GRADE 0	6/15/2011 10:51 AM	Disagree	GRADE 1	Possibly
KPS	100%	6/15/2011 10:55 AM	Agree	GRADE 1	N/A
MUCOSITIS/STOMATITIS	GRADE 1	6/15/2011 10:54 AM	Agree	GRADE 2	N/A
MYALGIA	GRADE 1	6/15/2011 10:51 AM	Agree	GRADE 3	N/A
NAUSEA	GRADE 0	6/15/2011 10:54 AM	Agree	GRADE 4	N/A
PAIN	GRADE 0	6/15/2011 10:51 AM	Agree	GRADE 0	N/A
SENSORY NEUROPATHY	GRADE 1	6/15/2011 10:50 AM	Agree	GRADE 1	N/A
VOICE CHANGES/HOARSENESS	GRADE 1	6/15/2011 10:54 AM	Agree	GRADE 1	N/A

Lock Submit

PRO-CTCAE

- Item library developed by the U.S. NCI
- 124 items representing 78 AEs
- Rigorously developed (Basch: JNCI, 2014)
- Robust measurement properties
  - Stakeholder input (Bruner: Trans Behav Med, 2011)
  - Content validity (Hay: Qual Life Res, 2014)
  - Validity, reliability, responsiveness (Dueck: ASCO, 2012)
  - Mode equivalence: paper/web/IVR (Bennett: ISOQOL, 2013)
  - Recall (Mendoza: ISOQOL, 2014)

http://healthcaredelivery.cancer.gov/resource/outcomes.html

JNCI JOURNAL OF THE NATIONAL CANCER INSTITUTE

PRO CONSORTIUM CRITICAL PATH INSTITUTE

Development of the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

Ethan Basch, Bryce B. Reeve, Sandra A. Mitchell, Steven B. Clauser, Lori M. Minasian, Amylou C. Dueck, Tito R. Mendoza, Jennifer Hay, Thomas M. Atkinson, Amy P. Abernethy, Deborah W. Bruner, Charles S. Cleeland, Jeff A. Sloan, Ram Chilukuri, Paul Baumgartner, Andrea Denicoff, Diane St. Germain, Ann M. O'Mara, Alice Chen, Joseph Kelaghan, Antonia V. Bennett, Laura Sit, Lauren Rogak, Allison Barz, Diane B. Paul, Deborah Schrag

Manuscript received October 14, 2013; revised June 24, 2014; accepted July 1, 2014.

Correspondence to: Ethan Basch, MD, MSc, Cancer Outcomes Research Program Lineberger, Comprehensive Cancer Center, University of North Carolina, 170 Manning Drive, Chapel Hill, NC 27514 (e-mail: ebasch@med.unc.edu).

The standard approach for documenting symptomatic adverse events (AEs) in cancer clinical trials involves investigator reporting using the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE). Because this approach underdetects symptomatic AEs, the NCI issued two contracts to create a patient-reported outcome (PRO) measurement system as a companion to the CTCAE, called the PRO-CTCAE. This Commentary describes development of the PRO-CTCAE by a group of multidisciplinary investigators and patient representatives and provides an overview of qualitative and quantitative studies of its measurement properties. A systematic evaluation of all 790 AEs listed in the CTCAE identified 78 appropriate for patient self-reporting. For each of these, a PRO-CTCAE plain language term in English and one to three items characterizing the frequency, severity, and/or activity interference of the AE were created, rendering a library of 124 PRO-CTCAE items. These items were refined in a cognitive interviewing study among patients on active cancer treatment with diverse educational, racial, and geographic backgrounds. Favorable measurement properties of the items, including construct validity, reliability, responsiveness, and between-mode equivalence, were determined prospectively in a demographically diverse population of patients receiving treatments for many different tumor types. A software platform was built to administer PRO-CTCAE items to clinical trial participants via the internet or telephone interactive voice response and was refined through usability testing. Work is ongoing to translate the PRO-CTCAE into multiple languages and to determine the optimal approach for integrating the PRO-CTCAE into clinical trial workflow and AE analyses. It is envisioned that the PRO-CTCAE will enhance the precision and patient-centeredness of adverse event reporting in cancer clinical research.

JNCI J Natl Cancer Inst (2014) 106(9): dju244 doi:10.1093/jnci/dju244

Example Item

CTCAE/MedDRA Term	*CTCAE Grade 1*	*CTCAE Grade 2*	*CTCAE Grade 3*	*CTCAE Grade 4*
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

Two Items	Responses
What was the <u>severity</u> of your **MOUTH OR THROAT SORES** at their worst?	None Mild Moderate Severe Very Severe
How much did **MOUTH OR THROAT SORES** <u>interfere</u> with your usual 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

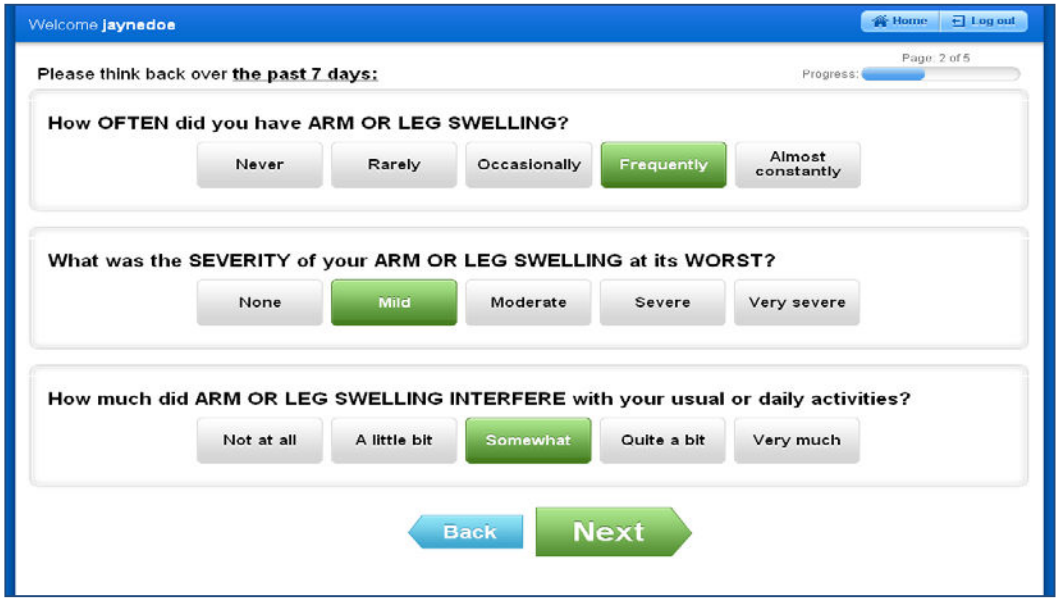
Cardio/Circulatory
- Swelling*
- Heart Palpitations

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

For more information, visit:
http://healthcaredelivery.cancer.gov/resource/outcomes.html

Feasibility

- >90% adherence with various self-report modes + human backup
  - Weekly web
  - Weekly IVR
  - In-clinic tablets



How is it Being Used?

- Under MTA with NCI*
  - Across phases of research
- Administration:
  - Weekly is standard (every 2 or 3 weeks may be considered; may have more measurement error)
  - Various modes
  - Backup human phone call
- Relationship with clinician CTCAE reports:
  - Shared vs. not shared
- Analysis/Reporting:
  - Similar to clinician-graded AEs
  - Incorporate change from baseline scores

**For more information contact: NCI Outcomes Research Branch*

Potential Uses

- Early-phase trials
  - Determine MTD; characterize AEs
- Pivotal trials
  - Characterize AEs; comparative tolerability
- Post marketing / registries
  - Understand real-world and longer-term impact

http://healthcaredelivery.cancer.gov/resource/outcomes.html

JAMA Oncology

Special Communication

Patient-Reported Outcomes in Cancer Drug Development and US Regulatory Review

Perspectives From Industry, the Food and Drug Administration, and the Patient

Ethan Basch, MD, MSc; Cindy Geoghegan, BA; Stephen Joel Coons, PhD; Ari Gnanasakthy, MSc, MBA; Ashley F. Slagle, PhD; Elektra J. Papadopoulos, MD, MPH; Paul G. Kluetz, MD

Data reported directly by patients about how they feel and function are rarely included in oncology drug labeling in the United States, in contrast to Europe and to nononcology labeling in the United States, where this practice is more common. Multiple barriers exist, including challenges unique to oncology trials, and industry's concerns regarding cost, logistical complexities, and the Food and Drug Administration's (FDA's) rigorous application of its 2009 guidance on the use of patient-reported outcome (PRO) measures. A panel consisting of representatives of industry, FDA, the PRO Consortium, clinicians, and patients was assembled at a 2014 workshop cosponsored by FDA to identify practical recommendations for overcoming these barriers. Key recommendations included increasing proactive encouragement by FDA to clinical trial sponsors for including PROs in drug development programs; provision of comprehensive PRO plans by sponsors to FDA early in drug development; promotion of an oncology-specific PRO research agenda; development of an approach to existing ("legacy") PRO measures, when appropriate (focused initially on symptoms and functional status); and increased FDA and industry training in PRO methodology. FDA has begun implementing several of these recommendations.

JAMA Oncol. doi:10.1001/jamaoncol.2015.0530
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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Ethan Basch, MD, MSc, Cancer Outcomes Research Program, Lineberger Comprehensive Cancer Center, University of North Carolina, 170 Manning Dr, Chapel Hill, NC 27599 (ebasch@med.unc.edu).

Discussion and/or Questions?

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