Protokoll des 2. APF Statistikleitertreffens am 2. Oktober 2015 bei Bayer / Berlin

Das 2. APF Statistikleitertreffen fand am 2. Oktober 2015 bei Bayer in Berlin mit rund 20 Teilnehmern aus Industrie, CROs und Universitäten statt.

1. Frank Langer: Einführung und Begrüßung

Grußworte von Frank Langer und Torsten Westermeier (als Gastgeber)

Erinnerung an und Präzisierung des Konzepts der APF Statistikleitertreffen (FL):

- Austausch zu wichtigen, für die Praxis relevanten Themen
- Konzeption von APF-Treffen durch Anregen aktueller, relevanter Themenschwerpunkte und potentieller Beiträge
- Anregen und Koordinieren von Beiträgen praktizierender Statistiker/ APF-Mitglieder zu Biometrischem Kolloquium, GMDS, etc.
- Organisation/Beteiligung von speziellen APF-Arbeitsgruppen, z.B. zur Kommentierung von Guidelines oder zu Stellungnahmen

2. Hans-Jürgen Lomp: Was hat sich seit dem letzten Treffen getan – Update zu den vereinbarten Schwerpunkten

- Implementierung von R in Clinical Reporting Environment, kurze Beschreibung des Status bei Boehringer Ingelheim (standard set-up, Zugriff auf Studiendaten – SDTM und SAS-ADS, Interaktion zwischen SAS und R – z.B. via SAS IML, Management von R-Output und program code, „approved“ R addon packages, Versionskontrolle)
- Probleme:
    - wie können „high quality“ R addon packages identifiziert werden?
    - Verwendung von R unter GxP (testing documentaton? keine standard IQ-OQ routine mitgeliefert, Validierung – re-programming? Einbeziehung kommerzieller Anbieter zur Lösung dieser Probleme (R-revolution)? – all dies Probleme, die unter SAS nicht auftreten, weil z.B. testing documentation auf Anfrage bereit gestellt werden kann)
    - geplant: „expert user discussion“ – Interessenten melden sich bei HJL
- Transparency (premature withdrawal from treatment vs. premature withdrawal from study)
    - Definition des “participant flow” (EudraCT / ct.gov)
    - Reasons for withdrawal/non-completion (from treatment/study?) unterschiedlich zw. EudraCT und ct.gov

3. Christoph Gerlinger: EFSPI Regulatory Committee meets MHRA – Update
   → "CGerlinger Update on meeting of EFSPI-PSI committee with NHRA.pdf"

4. Frank Langer: Analyse von AEs im Time-To-Event-Setting + Diskussion

- Diskrepanz zwischen ausgefeilten Methoden bei efficacy Analyse und „Steinzeit" bei Analyse von AEs – allgemeiner Konsens
- AEs bei ungleichen Expositionszeiten
- Analysen werden in unterschiedlichen Kontexten benötigt (z.B. Zulassung, Nutzenbewertung)
- Offensichtlich unterschiedliche Ansätze bevorzugt
- GBA: keine komplizierten Analysen!
- Methodische Probleme/Verzerrungspotential bekannt, z.B. bei time to first event (non-informative censoring → cumulative incidence)
- Verzerrt hinsichtlich welchen Estimands?
- Tim Friede: unterschiedliche Ansätze bei „Klinikern" in Pharma-Unternehmen und „Klinikern" in der Klinik
- Dietrich Knörzer: Fragebogen aus Patientensicht (wie von GBA angeregt), zB PRO-CTCAE
  → „2015_PRO_CTCAE_Validation.pdf"
- Tim Friede: weist auf die AWMF hin (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*; berät über grundsätzliche und fachübergreifende Angelegenheiten und Aufgaben, erarbeitet Empfehlungen und Resolutionen, befasst sich mit Problemstellungen, die alle medizinischen Fachgebiete gleichermaßen betreffen)
- Armin Schüler: Zusammenhang mit Estimands, benefit-risk
- bei Interesse: Meldung an FL

5. Hans-Jürgen Lomp: Estimands + allg. Diskussion

- kein update zu ICH E9 geplant, aber Addendum mit Q&A (vgl. ICH E3)
- Zeitpunkt des Reviews noch nicht klar
- Tim Friede: www.missingdata.org.uk mit div. Macros und Details zu Carpenter / Kenward *Multiple imputation and its application*
- *Missing data in randomized controlled trials — a practical guide* von Carpenter / Kenward frei zum download verfügbar: http://missingdata.lshtm.ac.uk/downloads/rm04_jh17_mk.pdf
- Notes from the PSI / EFSPI meeting on Estimands – GSK-September 2015 – Details und Präsentationen abrufbar unter http://www.psiweb.org/events/event-item/2015/09/28/default-calendar/european-statistical-meeting-on-estimands

6. DAGstat-/PSI-Treffen

Allgemeine Diskussion mit Themenvorschlägen

- Estimands + case studies + Kontext (zB Onkologie / Contraception)
- AEs (siehe 4.)
- multiple imputation
- Einbeziehung der „Ränder“: non-interventional studies, registries
- Reproduzierbarkeit von frühen Forschungsergebnissen
- statistical issues in reimbursement
- für APF:
    - responder placebo Modelle
    - real world evidence
    - AWMF (siehe 4.)
    - Estimands
- APF Herbstworkshop (2016) in Berlin (PAREXEL), Termin noch festzusetzen

7. Festlegung des nächsten Treffens

Novartis (Christian Sieder), Termin noch festzusetzen

EFSPI

European Federation of Statisticians in the Pharmaceutical Industry

Promoting Professional Standards in Europe

Update on Meeting of EFSPI/PSI Regulatory Committee with MHRA statisticians

London 2015-09-14

Dr. Christoph Gerlinger
EFSPI regulatory chair

EFSPI/PSI Regulatory Affairs Committee

- Co-ordinates review of regulatory guidance within EFSPI members
- Chair Christoph Gerlinger (EFSPI), co-chair Lesley France (PSI)
- Members
  - UK: Alan Phillips, Alun Bedding, Chrissie Fletcher, Daniel Evans, Frances Lynn, Jon Blatchford, Julie Anderson, Jürgen Hummel, Kerry Gordon, Lesley France
  - BE: Anne Danniau; DE: Christoph Gerlinger, Ruthild Sautermeister; DK: Per Larsson; FR: Maylis Coste
  - Companies: Amgen, AZ, Bayer, Biogen, BI, Grünenthal, GSK, Icon, Medicomp, Novo, Pfizer, Quintiles, Roche, Servier

Meeting with MHRA statisticians

- Informal meeting between statisticians
- Questions sent in advance to MHRA
- Summary of discussions published in SPIN (PSI newsletter) and EFSPI newsletter

Topics discussed

- follow up activities discussed previously
  - Best practices for modelling and simulation (presented at the 2015 PSI Conference)
  - Reach out to Small and Medium Enterprises (SMEs) to increase awareness of key statistical principles fundamental to drug development and how SMEs can seek statistical advice
  - Estimands: Disseminate concept to clinicians

Topics discussed (2)

- subgroup analyses
- post-authorisation efficacy studies
- methods for dose response evaluation
- recent experiences of parallel scientific advice involving regulators and/or payers

Topics discussed (3)

- data transparency
- use of Bayesian approaches in confirmatory trials
- comparison between Europe and US of initiatives aimed to accelerate the development of promising new medicines and biosimilars

EFSPI

European Federation of Statisticians in the Pharmaceutical Industry

Promoting Professional Standards in Europe

Upcoming Meeting of EFSPI/PSI Regulatory Committee with BSWP

London 2015-10-09

Upcoming meeting with BSWP

Draft agenda - BSWP Interested Parties meeting with Industry Associations' Statisticians

09 October 2015 from 14.00 to 15.30 and room 02-E

Chair: David Jonathan Wright

Item	Topic
1.	**Introduction and general topics**
2.	**Measurement of treatment benefit in a survival setting**
3.	**ICH E9 Addendum on estimands and sensitivity analysis**
4.	**Multiplicity**

Upcoming meeting with BSWP

Item	Topic
1	**General topics**
	Update on the actions taken by EFSPI/PSI in response to The July 2015 meeting with BSWP: • EFSPI recognises the need to educate the Statistics community on the best practice for subgroups. EFSPI has formed a cross-industry working group working to discuss and develop a best practice for subgroup analysis. EFSPI is also planning training events on subgroups; one will be at the next PSI conference in Berlin. • EFSPI has formed an expert group on estimands to support the EFPIA drafting representatives and to have taken steps to better inform the community on estimands. This includes presentations at the PSI conference, drafting a paper and an EFSPI meeting planned for 28th September 2015. What are the current statistical issues and potential regulatory statistical concerns of the future? Are there any areas that PSI/EFSPI should be leading to improve quality and standards across the industry?

Upcoming meeting with BSWP

Item	Topic
2	**Measurement of treatment benefit in a survival setting**
	In particular, treatment estimators, OS/PFS consistency, and definition of data maturity.

Upcoming meeting with BSWP

Item	Topic
3	**ICH E9 Addendum on estimands and sensitivity analysis**
	The requirements for improved clarity of the estimands and targeted sensitivity analysis are being widely discussed in the statistical arena. What steps need to be taken to engage/educate the broader clinical development community? In a situation where there are effective alternative medications which the active or the control arm could switch to on treatment failure for efficacy or safety, how the different estimands ('de facto' or 'de jure') to aid interpretation of the results can be prioritised? Will the proposed analysis framework differentiate between different estimators of the same estimand as opposed to estimators of different estimands? How will the use of different estimands be reflected in product labelling in the future. May the labelling information include results for more than one estimand? May the labelling information be based on a less conservative analysis/estimand than the one that was used to demonstrate that the product was effective? What would be the preferred estimand for safety data? Should e.g. MMRM analyses be used for safety data to describe the effect of drug if taken as prescribed?

Upcoming meeting with BSWP

Item	Topic
4	**Multiplicity**
	Can the BSWP provide an update on the progress of the new draft guideline for multiplicity? What are the key issues that the BSWP is seeking to address? Will the focus of this document be on requiring strong control for label claims? There seems to be a discrepancy between Europe and the US in the need for minimal alpha adjustments after an interim analysis. E.g., a stopping rule for overwhelming efficacy, such as the Peto rule of P <= 0.001 two-sided, has a minimal the effect on the final analysis. Does the BSWP request a correction in any case or is there some threshold as it appears to be the case in the US?

Recommened reading

COMMENT

Assessing the relative efficacy of new drugs: an emerging opportunity

Hans-Georg Eichler[1], Andrew Thomson[1], Irmgard Eichler[1] and Sebastian Schneeweiss[2]

The increasing availability of individual-level data from clinical trials could allow the relative efficacy of new drugs to be assessed in a robust, cost-effective and timely way.

Nat Rev Drug Discov. 2015 Jul;14(7):443-4

Original Investigation

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

Amylou C. Dueck, PhD; Tito R. Mendoza, PhD; Sandra A. Mitchell, PhD, CRNP, AOCN; Bryce B. Reeve, PhD; Kathleen M. Castro, RN, MS, AOCN; Lauren J. Rogak, MA; Thomas M. Atkinson, PhD; Antonia V. Bennett, PhD; Andrea M. Denicoff, MS, RN, ANP; Ann M. O'Mara, PhD, RN, FAAN; Yuelin Li, PhD; Steven B. Clauser, PhD, MPA; Donna M. Bryant, MSN, ANP-BC, OCN, CCRC; James D. Bearden III, MD, FACP; Theresa A. Gillis, MD; Jay K. Harness, MD; Robert D. Siegel, MD, FACP; Diane B. Paul, AAS; Charles S. Cleeland, PhD; Deborah Schrag, MD, MPH; Jeff A. Sloan, PhD; Amy P. Abernethy, MD, PhD; Deborah W. Bruner, RN, PhD, FAAN; Lori M. Minasian, MD, FACP; Ethan Basch, MD, MSc; for the National Cancer Institute PRO-CTCAE Study Group

IMPORTANCE To integrate the patient perspective into adverse event reporting, the National Cancer Institute developed a patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).

OBJECTIVE To assess the construct validity, test-retest reliability, and responsiveness of PRO-CTCAE items.

DESIGN, SETTING, AND PARTICIPANTS A total of 975 adults with cancer undergoing outpatient chemotherapy and/or radiation therapy enrolled in this questionnaire-based study between January 2011 and February 2012. Eligible participants could read English and had no clinically significant cognitive impairment. They completed PRO-CTCAE items on tablet computers in clinic waiting rooms at 9 US cancer centers and community oncology practices at 2 visits 1 to 6 weeks apart. A subset completed PRO-CTCAE items during an additional visit 1 business day after the first visit.

MAIN OUTCOMES AND MEASURES Primary comparators were clinician-reported Eastern Cooperative Oncology Group Performance Status (ECOG PS) and the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (QLQ-C30).

RESULTS A total of 940 of 975 (96.4%) and 852 of 940 (90.6%) participants completed PRO-CTCAE items at visits 1 and 2, respectively. At least 1 symptom was reported by 938 of 940 (99.8%) participants. Participants' median age was 59 years; 57.3% were female, 32.4% had a high school education or less, and 17.1% had an ECOG PS of 2 to 4. All PRO-CTCAE items had at least 1 correlation in the expected direction with a QLQ-C30 scale (111 of 124, $P < .05$ for all). Stronger correlations were seen between PRO-CTCAE items and conceptually related QLQ-C30 domains. Scores for 94 of 124 PRO-CTCAE items were higher in the ECOG PS 2 to 4 vs 0 to 1 group (58 of 124, $P < .05$ for all). Overall, 119 of 124 items met at least 1 construct validity criterion. Test-retest reliability was 0.7 or greater for 36 of 49 prespecified items (median [range] intraclass correlation coefficient, 0.76 [0.53-.96]). Correlations between PRO-CTCAE item changes and corresponding QLQ-C30 scale changes were statistically significant for 27 prespecified items (median [range] $r = 0.43$ [0.10-.56]; all $P \leq .006$).

CONCLUSIONS AND RELEVANCE Evidence demonstrates favorable validity, reliability, and responsiveness of PRO-CTCAE in a large, heterogeneous US sample of patients undergoing cancer treatment. Studies evaluating other measurement properties of PRO-CTCAE are under way to inform further development of PRO-CTCAE and its inclusion in cancer trials.

JAMA Oncol. doi:10.1001/jamaoncol.2015.2639
Published online August 13, 2015.

Invited Commentary

Supplemental content at jamaoncology.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: National Cancer Institute PRO-CTCAE Study Group members are listed at the end of the article.

Corresponding Author: Amylou C. Dueck, PhD, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ 85259 (dueck@mayo.edu).

In cancer clinical trials, adverse events (AEs) are collected and reported using the US National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE).[1] The CTCAE is a library of items representing 790 discrete AEs, each graded using an ordinal severity scale.[2] Approximately 10% of AEs in the CTCAE are symptoms (eg, nausea, sensory neuropathy), which in trials have historically been reported by clinical investigators.[3] However, there is empirical evidence that collection of this information directly from patients improves the precision and reliability of symptomatic AE detection in trials[4-9] and is feasible.[10,11] Moreover, there is substantial evidence that clinical investigators may miss up to half of patients' symptomatic AEs.[5,6,12,13]

To improve precision and patient-centeredness in the capture of symptomatic AEs, the NCI developed a library of patient-reported outcome (PRO) items to supplement the CTCAE, called the PRO-CTCAE,[14] as has been previously described.[15] Of the 790 AEs in the CTCAE, 78 were identified as amenable to patient self-report. For each of these AEs, PRO items were created reflecting the attributes of frequency, severity, interference with usual or daily activities, amount, or presence or absence. For any given AE, 1 to 3 attributes were selected depending on the content of the CTCAE criteria for that AE and the nature of that particular AE. In total, 124 individual items represent the 78 symptomatic AEs currently in the PRO-CTCAE item library.

The generic structure for PRO-CTCAE items and response options is shown in **Table 1**. Each item includes a plain language term for the AE, the attribute of interest, and the standard recall period of "the past 7 days." Cognitive interviews previously determined a high level of patient understanding and meaningfulness of the items.[16] Software was developed for administering PRO-CTCAE items to patients either via World Wide Web or an automated telephone interactive voice response interface, and was refined through usability testing.[15,17]

For any new measurement tool in clinical research (eg, biomarkers, imaging, diagnostic test), it is essential to establish that the new instrument accurately and reliably captures the underlying phenomenon that it is intended to measure. To accomplish this for the PRO-CTCAE, this study was designed to evaluate the measurement properties of the 124 items in the PRO-CTCAE item library including validity (degree to which an instrument accurately measures the underlying phenomenon), reliability (ability of an instrument to produce similar scores on repeated measurements under similar conditions), and responsiveness (capacity of an instrument to show a change when there has been a change in the underlying phenomenon). These properties were examined individually for each item because PRO-CTCAE items are individually reported in trials and not aggregated into a single score. Inclusion of patients with diversity with respect to cancer type, treatment modality, and sociodemographic characteristics was considered essential given the intended use of PRO-CTCAE across varying research contexts. To simultaneously evaluate the measurement properties of 124 items within a single study required us to use a varied set of comparators or "anchors" and warranted a larger and more diverse sample of respondents and settings than is typically used in most validation studies of fixed-length PRO measures.

At a Glance

- Symptomatic adverse events (AEs) in cancer trials are currently graded by clinicians using the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE).
- This study assessed the measurement properties (validity, reliability, and responsiveness) of the newly developed NCI Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE).
- A total of 940 adults with cancer undergoing outpatient cancer treatment provided PRO-CTCAE and other patient-reported and clinical data.
- Most of the PRO-CTCAE items (119 of 124) met at least a validity criterion.
- The PRO-CTCAE provides a valid and reliable assessment of symptomatic toxic effects from the patient's perspective and is encouraged for use in oncology trials to enhance the accuracy of AE reporting.

Table 1. Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Item Formats[a]

Please think back over the past 7 days:	Example
Frequency (25 symptomatic AE terms): How **often** did you have _____? Never/Rarely/Occasionally/Frequently/Almost constantly	Vomiting
Severity (51 symptomatic AE terms): What was the **severity** of your _____ at its worst? None/Mild/Moderate/Severe/Very severe	Pain
Interference (25 symptomatic AE terms): How much did _____ **interfere** with your usual or daily activities? Not at all/A little bit/Somewhat/Quite a bit/Very much	Sudden urges to urinate
Presence (21 symptomatic AE terms): Did you have any _____? No/Yes	Unusual darkening of the skin
Amount (2 symptomatic AE terms): Did you have any _____? Not at all/A little bit/Somewhat/Quite a bit/Very much	Hair loss

Abbreviation: AE, adverse event.

[a] See Basch et al[15] for a complete listing of PRO-CTCAE items.

Methods

Patients

Adult patients initiating or undergoing outpatient chemotherapy, radiation therapy, or both at 1 of 9 US cancer centers or community oncology practices were approached in clinical waiting areas and invited to participate in this study. Participating sites with number of patients enrolled included Dana-Farber Cancer Institute, Boston, Massachusetts (n = 40); Hartford Hospital-Helen and Harry Gray Cancer Center, Hartford, Connecticut (n = 104); Helen F. Graham Cancer Center and Research Institute at Christiana Care Health System, Newark, Delaware (n = 105); Mayo Clinic, Rochester, Minnesota (n = 9); Memorial Sloan Kettering Cancer Center, New York, New York (n = 280); Our Lady of the Lake and Mary Bird Perkins Cancer Center, Baton Rouge, Louisiana (n = 133); Gibbs Cancer Center, Spartanburg, South Carolina (n = 113); St Joseph Hospital of Orange, Orange, California (n = 104); and University of Texas M. D. Anderson Cancer Center, Houston (n = 52).

Eligibility criteria required that all participants be able to read and comprehend English, be without clinically significant cognitive impairment on the basis of site investigator judgment, have a cancer diagnosis, and be actively undergoing cancer treatment or be initiating treatment within the next 7 days. Patients with any cancer type were eligible, but an accrual strategy was used to enrich for specific cancer types to facilitate planned comparisons between groups based on cancer type in the validity analysis, including breast, aerodigestive tract (head/neck and esophageal cancer), genitourinary (prostate and bladder), lung, colorectal, and lymphoma or myeloma. An enrichment strategy was also used to ensure that a minimum of 15% of participants had impaired performance status (PS), defined as Eastern Cooperative Oncology Group (ECOG) PS of at least 2.

Study sites were selected to encompass geographic, racial/ethnic, economic, and educational diversity reflective of the US population with the understanding that the requirement to be English speaking would limit the enrollment of Hispanic patients (a separate study evaluating the Spanish language version of the PRO-CTCAE has been conducted[18]). Race/ethnicity was self-reported by patients.

Institutional review board approval was obtained at all sites and at the NCI, and all patients provided written informed consent. Each participant received a $20 gift card or parking voucher.

Questionnaire

The previously developed PRO-CTCAE item library consists of 78 symptomatic AEs represented by 124 distinct items.[14,15] To limit burden, a maximum of 58 symptomatic AEs (82 items) was presented to each participant. Seven electronic surveys targeted toward different cancer types (eTable 1 in the Supplement) were created in the central PRO-CTCAE web survey administration platform. As part of the registration process, the site coordinator selected a single survey on the basis of the patient's diagnosis, and that survey was then automatically scheduled for completion at each visit. All surveys included a set of 20 "core" symptomatic AEs,[15] predetermined on the basis of high prevalence across cancer types in prior NCI-sponsored clinical trials.[19] Remaining symptomatic AEs were classified a priori as likely to be prevalent or nonprevalent in specific cancer types on the basis of expert consultation, patient representative input, and literature review. These items were included on surveys for selected cancer types to facilitate planned comparisons between groups based on cancer type. When 80% of accrual was reached, to increase sample size for the 58 symptomatic AEs that were not systematically administered to all patients, a new survey containing exactly these 58 symptomatic AEs was administered to all subsequently enrolled patients.

Procedure

The PRO-CTCAE items were completed by participants prior to clinic appointments on tablet computers via the PRO-CTCAE measurement system hosted on a secure server at the NCI.[17] To optimize usability by individuals with disabilities, PRO-CTCAE software is compliant with Section 508 of the US Rehabilitation Act. The PRO-CTCAE measurement system uses conditional branching for AEs that contain more than a single attribute, such that subsequent items about severity or interference are skipped if respondents indicate that they are not experiencing a specific symptomatic AE. Participants were required to answer questions without assistance but could request technical assistance with using the tablet computer from study staff.

Anchors

Anchors are measurable criteria prespecified as comparators in an instrument validation study. Examples of anchors relevant in PRO validation studies include well-validated patient- and clinician-reported outcomes and clinical variables such as disease site or concurrent medication use. For this study, anchors selected a priori included both generic measures (eg, patient-reported global health-related quality of life [HRQOL] or clinician-reported PS) and more specific clinical variables (eg, antiemetic use or receipt of taxane chemotherapy). These anchors were selected on the basis of literature review, expert consensus, and patient representative input.

The PRO anchors were administered to participants using a paper booklet containing the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30),[20] a 30-item instrument that produces an HRQOL summary score,[21,22] a global health status/quality of life (QOL) scale score, 5 functioning (physical, role, emotional, social, cognitive) scale scores, and 9 selected symptom item/scale scores. There are 28 items measured on a 1 to 4 scale (1 = not at all; 4 = very much), with the remaining 2 items (overall health and QOL) scored on a 1 to 7 scale (1 = very poor; 7 = excellent). Like PRO-CTCAE, the recall period for the QLQ-C30 is "the past week." Patients also completed 3 Global Impression of Change (GIC)[23,24] items at the primary follow-up visit. These items asked patients to rate their changes in overall QOL, physical condition, and emotional state on a 7-point scale ranging from "very much better," "moderately better," "a little better," "about the same," "a little worse," "moderately worse," to "very much worse."

Clinician-reported ECOG PS was collected at each visit via a case report form. Other clinical anchors were abstracted from medical records and included whether the participant had received radiation therapy, surgery, and/or chemotherapy in the prior 2 weeks; type of chemotherapy; and use of specific medication classes, including hormonal therapy, narcotic analgesics, laxatives or stool softeners, antiemetics, sleep aids, antidiarrhea medications, antacids, bronchodilators or inhaled corticosteroids, anxiolytics, and/or antidepressants.

Study Visits

Participants were assigned to 1 of 3 groups with differing questionnaire schedules based on cancer type and clinic visit schedule, to avoid the necessity of extra clinic visits in this symptomatic population (eFigure 1 in the Supplement). Group A included patients undergoing daily radiation or chemoradiation therapy to enable analyses of test-retest reliability and varying recall periods (recall period analyses will be reported separately).[25] Group B included patients with at least 4 planned consecutive weekly clinic visits. Group C included participants whose planned clinic visits precluded participation in group B but who did have a return clinic visit planned within

1 to 6 weeks. Irrespective of group assignment, all patients completed PRO-CTCAE items and QLQ-C30 at 2 visits that were spaced approximately 1 to 6 weeks apart. At each visit, ECOG PS and other clinical anchors were recorded on case report forms. The PRO-CTCAE surveys administered to patients in group A on the business day following study day 1 were used for the analysis of test-retest reliability, and included 49 prespecified PRO-CTCAE items.

Statistical Analysis

Construct validity reflects the association between a new measurement tool and an established measure of the underlying concept(s) of interest. Construct validity is often investigated through convergent validity, which determines whether the new measure moves in the same direction as an established instrument, and known-groups validity, which determines whether the measurement tool can distinguish between groups of patients who are thought to be distinct with respect to the underlying concept being measured. To assess convergent validity, Pearson correlations were computed between each PRO-CTCAE item and QLQ-C30 HRQOL summary and other functioning/symptom scale scores. To aid interpretation, QLQ-C30 HRQOL summary and functioning/global scales were reverse scored such that higher scores represent inferior outcomes, matching the direction of PRO-CTCAE items. Pearson correlation values of 0.1, 0.3, and 0.5 were interpreted as small, medium, and large.[26(pp19-108)] To assess known-groups validity, 2-sample *t* tests for ordinal 0 to 4 scales and χ^2 tests for binary scales were used to compare each PRO-CTCAE item between patients with high and low PS (ECOG PS 0-1 vs 2-4). Additional known-groups analyses were prespecified for PRO-CTCAE items that were expected to be higher in 1 group of patients vs another on the basis of cancer type, treatment, or other clinically relevant characteristic (eg, pain in the abdomen in patients with gastrointestinal vs lung cancers). Effect sizes (computed as the difference between group means divided by the pooled standard deviation [Cohen *d*], or difference between twice the arcsine of the square root of each sample proportion [Cohen *h*]) of 0.2, 0.5, and 0.8 were interpreted as small, medium, and large, respectively.[26(pp19-108)]

Test-retest reliability was estimated using the intraclass correlation coefficient (ICC) based on a 1-way analysis of variance model[27] with an ICC of 0.7 or greater interpreted as high.[28(pp264-265)] Responsiveness of items was investigated by comparing change from first to second visit in 27 PRO-CTCAE items selected a priori. Comparisons were made using a 1-sided Jonckheere-Terpstra test across respondents who reported their GIC to be worse ("a little worse," "moderately worse," or "very much worse"), unchanged ("about the same"), or improved ("a little better," "moderately better," or "very much better").[29] Standardized response means (SRMs) were computed as the mean change score divided by the standard deviation of the change scores within each change category (worse vs no change vs improved) for each PRO-CTCAE item. Pearson correlations were also computed between PRO-CTCAE item changes and QLQ-C30 scale changes. One GIC item and 1 QLQ-C30 scale were specified a priori for each of the 27 PRO-CTCAE items. See eTable 2 in the Supplement for symptomatic AEs included in each analysis.

To accommodate conditional branching in the PRO-CTCAE software, values for automatically skipped items were assumed to be zero. $P < .05$ was considered statistically significant. To take into consideration potential collinearity and multiplicity, sensitivity analyses used a stricter cutoff of $P < .001$ and the Hochberg step-up procedure[30] across construct validity analyses within each item. An item was considered valid if statistical significance ($P < .05$) along with a meaningful effect size (Pearson $r \geq 0.1$ or group difference effect size d or $h \geq 0.2$) was observed for at least 1 convergent or known-groups validity analysis.

Results

Between January 2011 and February 2012, 975 patients initiating or undergoing chemotherapy and/or radiation therapy were enrolled, with 940 of 975 (96.4%) eligible patients completing PRO-CTCAE items at visit 1 and 852 of 940 (90.6%) completing PRO-CTCAE items at visit 2 (eFigure 1 in the Supplement). Characteristics of the 940 participants included in this analysis are presented in **Table 2**. Median (range) age was 59 (19-91) years, 539 (57.3%) were female, 161 (17.1%) had impaired PS (ECOG 2-4), and 305 (32.4%) had no more than a high school education.

Almost all participants (938 of 940) reported the presence of at least 1 symptom (ie, a score >0) during the 2 primary visits, with 768 of 940 (81.7%) reporting at least 1 symptom as frequent, severe, and/or interfering "quite a bit" with daily activities. Patients were broadly symptomatic, reporting presence of a median (range) of 23 (0-91) symptoms, with 904 of 940 (96.2%) reporting presence of 5 or more symptoms at the first visit. Of the 124 PRO-CTCAE items, 118 (95.2%) were reported as present by at least 10% of respondents at both primary visits, with 82 of 124 (66.1%) items having at least 25% prevalence. The distribution of item scores for the set of 20 "core" symptomatic AEs appears in eFigure 2 in the Supplement.

Detailed results related to construct validity of PRO-CTCAE items using all anchors are provided in eTable 3 in the Supplement. With respect to convergent validity, 122 of 124 (98.4%) PRO-CTCAE items were associated in the expected direction with the QLQ-C30 HRQOL summary score (102 of 124, $P < .05$ for all; 87 of 124, $P < .001$ for all) (**Figure 1**); 107 of 124 items demonstrated meaningful correlation (Pearson $r \geq 0.1$). When all QLQ-C30 functioning/global scales were considered, all 124 PRO-CTCAE items were associated in the expected direction with 1 or more scales, with 114 of 124 demonstrating meaningful correlation (Pearson $r \geq 0.1$), and 111 of 124 coefficients were statistically significant ($P < .05$ for all; 90 of 124, $P < .001$ for all). The PRO-CTCAE items that were likely to affect physical functioning had the strongest correlations with the QLQ-C30 physical functioning scale (eg, shortness of breath severity: Pearson $r = 0.47$, $P < .001$), whereas items likely to affect cognitive functioning had the strongest correlations with the QLQ-C30 cognitive functioning scale (eg, problems with concentration severity: Pearson $r = 0.71$, $P < .001$; problems with memory severity: Pearson $r = 0.69$, $P < .001$). Simi-

Table 2. Patient Characteristics

Characteristic	No. (%) (N = 940)
Age at enrollment, median (range), y	59 (19-91)
Age group, y, No. (%)	
<30	23 (2.5)
30-64	597 (63.5)
65-74	235 (25.0)
≥75	85 (9.0)
Sex, No. (%)	
Female	539 (57.3)
Male	401 (42.7)
Ethnicity, No. (%)	
Hispanic or Latino	56 (6.0)
Not Hispanic or Latino	832 (88.5)
Missing	52 (5.5)
Race, No. (%)	
White	675 (71.8)
Black or African American	203 (21.6)
Asian	42 (4.5)
Other or multiple races reported	8 (0.9)
Missing	12 (1.3)
Education, No. (%)	
High school or less	305 (32.4)
Some college	199 (21.2)
College graduate or more	415 (44.1)
Missing	21 (2.2)
Cancer type, No. (%)	
Lung, head, or neck	329 (35.0)
Breast	260 (27.7)
Genitourinary or gynecologic	172 (18.3)
Gastrointestinal	95 (10.1)
Hematologic	47 (5.0)
Other or unknown	37 (3.9)
ECOG performance status at first visit, No. (%)	
0-1	779 (82.9)
2-4	161 (17.1)
Cancer treatment in prior 2 wk, No. (%)	
Chemotherapy	522 (55.5)
Radiation	424 (45.1)
Surgery	35 (3.7)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

lar results were seen between PRO-CTCAE items and conceptually related QLQ-C30 emotional, role, and social functioning scales. For those PRO-CTCAE items with a parallel QLQ-C30 symptom scale/item (eg, fatigue), large correlations between analogous items (all Pearson $r > 0.69$, $P < .001$) were consistently observed.

In the known-groups comparison between patients with low and high PS, 94 of 124 PRO-CTCAE items had higher mean scores in the ECOG PS 2 to 4 group vs 0 to 1 group (58 of 124, $P < .05$ for all; 37 of 124, $P < .001$ for all; shown for 37 PRO-CTCAE items in eFigure 3 in the Supplement).

In 127 a priori known-groups comparisons involving 87 PRO-CTCAE items based on cancer type, treatment, or other clinically relevant characteristic, 110 of 127 comparisons demonstrated higher PRO-CTCAE scores in the group expected to have worse symptom experience (85 of 127, $P < .05$ for all; 53 of 127, $P < .001$ for all) (eTable 3 in the Supplement).

Most PRO-CTCAE items (119 of 124) had a statistically significant and meaningful effect size on 1 or more construct validity criteria. The 5 items that did not exhibit at least 1 statistically significant and meaningful effect had low prevalence in this sample, thereby limiting our analysis. These items were nosebleeds (prevalence, 15% [frequency] and 14% [severity]); pain, swelling, or redness at site of drug injection or intravenous therapy (prevalence, 13%); pain during vaginal sex (prevalence, 21%); and rash (prevalence, 17%). Most PRO-CTCAE items (99 of 124 and 101 of 124) remained statistically significant under stricter criteria ($P < .001$ and Hochberg $P < .05$, respectively) in sensitivity analyses (eTable 3 in the Supplement).

In the subset of 80 respondents who completed PRO-CTCAE on consecutive business days (median [range], 1 [1-3] days), the test-retest reliability for the 49 prespecified items ranged from 0.53 to 0.96 (median ICC, 0.76) with 36 of 49 items having an ICC of at least 0.7 (eTable 4 in the Supplement).

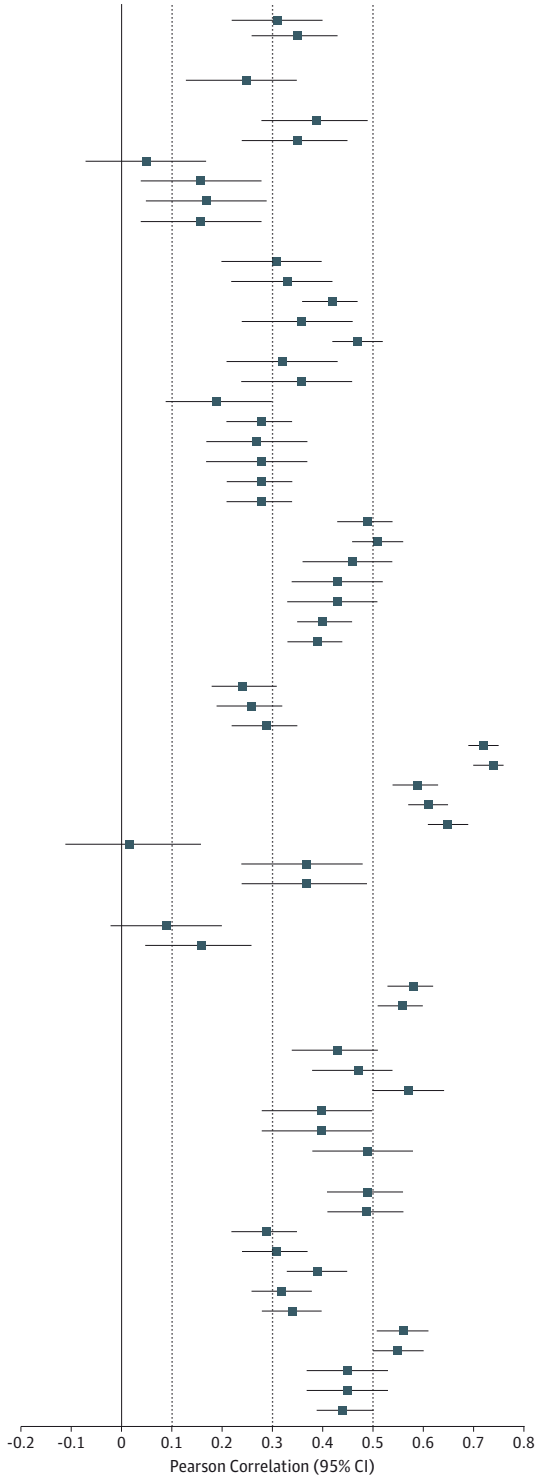
In the analysis of responsiveness (**Figure 2**), statistically significant ($P < .05$) monotonically decreasing mean PRO-CTCAE change scores were observed for 23 of 27 prespecified items ($P < .001$ for 13 items). The median (range) SRM in patients reporting worsening was 0.19 (0.03-0.40), whereas that in patients reporting improvement was −0.14 (−0.30 to 0.09). Statistically significant correlations were observed between PRO-CTCAE item changes and corresponding QLQ-C30 scale changes for all 27 prespecified items (median [range] r, 0.43 [0.10-0.56]; all $P \leq .006$).

Discussion

This large-scale multicenter study in adults undergoing active cancer therapy provides evidence supporting the validity, reliability, and responsiveness of the items in the PRO-CTCAE library. The PRO-CTCAE is unique in its intended use to complement the CTCAE by providing comprehensive data on symptomatic AEs in cancer clinical trials from the patient perspective.

The design of this study posed a unique methodological challenge, due to the goal of assessing, within a single investigation, the measurement properties of 124 individual items representing a broad spectrum of symptomatic toxic effects. Typically, PRO validation studies will test the properties of a single composite index score or a small number of domains that encompass related concepts. For the assessment of validity in the present study, the primary strategy to address this challenge was inclusion of both broad generic anchors (eg, global HRQOL, ECOG PS) and more specific clinical variables (eg, receipt of specific medication classes such as antiemetics). Interestingly, all of the PRO-CTCAE items were associated in the expected direction with at least 1 generic functioning measure, suggesting the impact that even a single toxic effect may have on the patient experience.

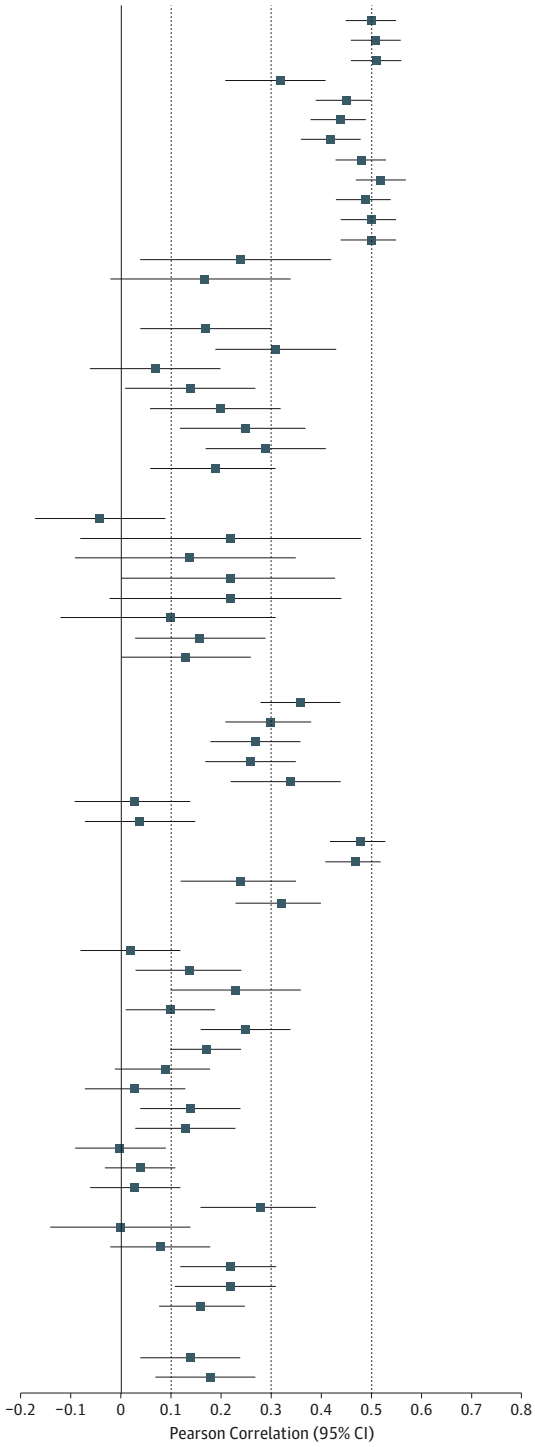
Figure 1. Pearson Correlations Between 124 Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Item Scores and European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) Health-Related Quality of Life Summary Score at Visit 1



	No.	Corr	(95% CI)
Cardiac disorders			
Pounding/racing heartbeat (F)	394	0.31	(0.22 to 0.40)
Pounding/racing heartbeat (S)	394	0.35	(0.26 to 0.43)
Ear and labyrinth disorders			
Ringing in ears (S)	286	0.25	(0.13 to 0.35)
Eye disorders			
Blurry vision (S)	261	0.39	(0.28 to 0.49)
Blurry vision (I)	261	0.35	(0.24 to 0.45)
Flashing lights in eyes (P)	260	0.05	(−0.07 to 0.17)
Spots/lines/floaters in eyes (P)	259	0.16	(0.04 to 0.28)
Watery eyes (S)	259	0.17	(0.05 to 0.29)
Watery eyes (I)	259	0.16	(0.04 to 0.28)
Gastrointestinal disorders			
Bloating (F)	320	0.31	(0.20 to 0.40)
Bloating (S)	320	0.33	(0.22 to 0.42)
Constipation (S)	825	0.42	(0.36 to 0.47)
Difficulty swallowing (S)	245	0.36	(0.24 to 0.46)
Dry mouth (S)	821	0.47	(0.42 to 0.52)
Heartburn (F)	244	0.32	(0.21 to 0.43)
Heartburn (S)	244	0.36	(0.24 to 0.46)
Increased passing of gas (P)	320	0.19	(0.09 to 0.30)
Loose stools (F)	796	0.28	(0.21 to 0.34)
Loss of control of bowel movements (F)	336	0.27	(0.17 to 0.37)
Loss of control of bowel movements (I)	337	0.28	(0.17 to 0.37)
Mouth or throat sores (S)	803	0.28	(0.21 to 0.34)
Mouth or throat sores (I)	801	0.28	(0.21 to 0.34)
Nausea (F)	814	0.49	(0.43 to 0.54)
Nausea (S)	813	0.51	(0.46 to 0.56)
Pain in the abdomen (F)	320	0.46	(0.36 to 0.54)
Pain in the abdomen (S)	320	0.43	(0.34 to 0.52)
Pain in the abdomen (I)	320	0.43	(0.33 to 0.51)
Vomiting (F)	805	0.40	(0.35 to 0.46)
Vomiting (S)	805	0.39	(0.33 to 0.44)
General disorders and administration site conditions			
Arm/leg swelling (F)	807	0.24	(0.18 to 0.31)
Arm/leg swelling (S)	807	0.26	(0.19 to 0.32)
Arm/leg swelling (I)	807	0.29	(0.22 to 0.35)
Fatigue (S)	855	0.72	(0.69 to 0.75)
Fatigue (I)	852	0.74	(0.70 to 0.76)
Pain (F)	827	0.59	(0.54 to 0.63)
Pain (S)	827	0.61	(0.57 to 0.65)
Pain (I)	827	0.65	(0.61 to 0.69)
Pain/swelling/redness at intravenous access (P)	201	0.02	(−0.11 to 0.16)
Shivering or shaking chills (F)	197	0.37	(0.24 to 0.48)
Shivering or shaking chills (S)	197	0.37	(0.24 to 0.49)
Injury, poisoning, and procedure complications			
Bruise easily (P)	305	0.09	(−0.02 to 0.20)
Skin burns from radiation (S)	330	0.16	(0.05 to 0.26)
Metabolism and nutrition disorders			
Decreased appetite (S)	820	0.58	(0.53 to 0.62)
Decreased appetite (I)	819	0.56	(0.51 to 0.60)
Musculoskeletal and connective tissue disorders			
Aching joints (F)	344	0.43	(0.34 to 0.51)
Aching joints (S)	344	0.47	(0.38 to 0.54)
Aching joints (I)	344	0.57	(0.50 to 0.64)
Aching muscles (F)	224	0.40	(0.28 to 0.50)
Aching muscles (S)	224	0.40	(0.28 to 0.50)
Aching muscles (I)	224	0.49	(0.38 to 0.58)
Nervous system disorders			
Dizziness (S)	393	0.49	(0.41 to 0.56)
Dizziness (I)	393	0.49	(0.41 to 0.56)
Headache (F)	816	0.29	(0.22 to 0.35)
Headache (S)	815	0.31	(0.24 to 0.37)
Headache (I)	815	0.39	(0.33 to 0.45)
Numbness/tingling in your hands or feet (S)	824	0.32	(0.26 to 0.38)
Numbness/tingling in your hands or feet (I)	824	0.34	(0.28 to 0.40)
Problems with concentration (S)	816	0.56	(0.51 to 0.61)
Problems with concentration (I)	816	0.55	(0.50 to 0.60)
Problems with memory (S)	358	0.45	(0.37 to 0.53)
Problems with memory (I)	358	0.45	(0.37 to 0.53)
Problems with tasting food/drink (S)	818	0.44	(0.39 to 0.50)

(continued)

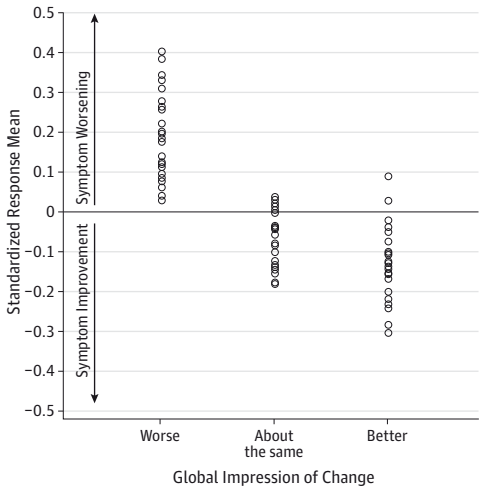
Figure 1. Pearson Correlations Between 124 Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Item Scores and European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) Health-Related Quality of Life Summary Score at Visit 1 (continued)



	No.	Corr	(95% CI)
Psychiatric disorders			
Anxiety (F)	816	0.50	(0.45 to 0.55)
Anxiety (S)	816	0.51	(0.46 to 0.56)
Anxiety (I)	816	0.51	(0.46 to 0.56)
Decreased sexual interest (S)	311	0.32	(0.21 to 0.41)
Feelings that nothing could cheer you up (F)	794	0.45	(0.39 to 0.50)
Feelings that nothing could cheer you up (S)	794	0.44	(0.38 to 0.49)
Feelings that nothing could cheer you up (I)	794	0.42	(0.36 to 0.48)
Insomnia (S)	834	0.48	(0.43 to 0.53)
Insomnia (I)	832	0.52	(0.47 to 0.57)
Sad or unhappy feelings (F)	819	0.49	(0.43 to 0.54)
Sad or unhappy feelings (S)	819	0.50	(0.44 to 0.55)
Sad or unhappy feelings (I)	819	0.50	(0.44 to 0.55)
Took too long to have an orgasm or climax (P)	97	0.24	(0.04 to 0.42)
Unable to have an orgasm or climax (P)	110	0.17	(−0.02 to 0.34)
Renal and urinary disorders			
Frequent urination (F)	220	0.17	(0.04 to 0.30)
Frequent urination (I)	219	0.31	(0.19 to 0.43)
Loss of control of urine (F)	219	0.07	(−0.06 to 0.20)
Loss of control of urine (I)	219	0.14	(0.01 to 0.27)
Pain or burning with urination (S)	212	0.20	(0.06 to 0.32)
Sudden urges to urinate (F)	216	0.25	(0.12 to 0.37)
Sudden urges to urinate (I)	216	0.29	(0.17 to 0.41)
Urine color change (P)	224	0.19	(0.06 to 0.31)
Reproductive system and breast disorders			
Breast area enlargement or tenderness (S)	238	−0.04	(−0.17 to 0.09)
Difficulty getting or keeping an erection (S)	45	0.22	(−0.08 to 0.48)
Ejaculation problems (F)	75	0.14	(−0.09 to 0.35)
Irregular menstrual periods (P)	75	0.22	(0.00 to 0.43)
Miss an expected menstrual period (P)	67	0.22	(−0.02 to 0.44)
Pain during vaginal sex (S)	82	0.10	(−0.12 to 0.31)
Unusual vaginal discharge (A)	215	0.16	(0.03 to 0.29)
Vaginal dryness (S)	215	0.13	(0.00 to 0.26)
Respiratory, thoracic, and mediastinal disorders			
Cough (S)	439	0.36	(0.28 to 0.44)
Cough (I)	439	0.30	(0.21 to 0.38)
Hiccups (F)	412	0.27	(0.18 to 0.36)
Hiccups (S)	412	0.26	(0.17 to 0.35)
Hoarse voice (S)	245	0.34	(0.22 to 0.44)
Nosebleeds (F)	304	0.03	(−0.09 to 0.14)
Nosebleeds (S)	303	0.04	(−0.07 to 0.15)
Shortness of breath (S)	811	0.48	(0.43 to 0.53)
Shortness of breath (I)	811	0.47	(0.42 to 0.52)
Voice changes (P)	244	0.24	(0.12 to 0.35)
Wheezing (S)	439	0.32	(0.23 to 0.40)
Skin and subcutaneous tissue disorders			
Acne (S)	391	0.02	(−0.08 to 0.12)
Bed sores (P)	318	0.14	(0.03 to 0.24)
Body odor (S)	197	0.23	(0.10 to 0.36)
Change in the color of fingernails/toenails (P)	465	0.10	(0.01 to 0.19)
Dry skin (S)	393	0.25	(0.16 to 0.34)
Hair loss (A)	794	0.17	(0.10 to 0.24)
Hand-foot syndrome (S)	438	0.09	(−0.01 to 0.18)
Hives (P)	391	0.03	(−0.07 to 0.13)
Increased skin sensitivity to sunlight (P)	391	0.14	(0.04 to 0.24)
Itchy skin (S)	393	0.13	(0.03 to 0.23)
Lose any fingernails/toenails (P)	465	0.00	(−0.09 to 0.09)
Rash (P)	800	0.04	(−0.03 to 0.11)
Ridges/bumps on fingernails/toenails (P)	465	0.03	(−0.06 to 0.12)
Skin cracking at the corners of your mouth (S)	244	0.28	(0.16 to 0.39)
Stretch marks (P)	197	0.00	(−0.14 to 0.14)
Unexpected decrease in sweating (P)	391	0.08	(−0.02 to 0.18)
Unexpected or excessive sweating (F)	358	0.22	(0.12 to 0.31)
Unexpected or excessive sweating (S)	358	0.22	(0.11 to 0.31)
Unusual darkening of the skin (P)	485	0.16	(0.08 to 0.25)
Vascular disorders			
Hot flashes (F)	359	0.14	(0.04 to 0.24)
Hot flashes (S)	359	0.18	(0.07 to 0.27)

See eTable 3 in the Supplement for all computed Pearson correlations between PRO-CTCAE items and EORTC QLQ-C30 functioning, global, and symptom scales. Dashed lines at 0.1, 0.3, and 0.5 correspond to small, medium, and large effect sizes according to Cohen.[26] A indicates amount; Corr, correlation; F, frequency; I, interference with usual or daily activities; P, presence/absence; S, severity.

Figure 2. Standardized Response Means Across 27 Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Items by Patient-Reported Global Impression of Change Category



Symbols show 27 frequency, severity, and interference items selected prior to initiation of the responsiveness analysis. The set of 20 "core" symptomatic adverse events (AEs) was reviewed and symptomatic AEs were selected if they had high potential to be meaningfully related to global changes in quality of life, physical condition, and/or emotional state (ie, the Global Impression of Change items that were administered at the second visit). Of the 20 reviewed symptomatic AEs, 13 were included on the basis of this criterion (see eTable 2 in the Supplement). The symptomatic AEs that were excluded were believed to be related to initiation or changes in specific treatments (dry mouth, problems with tasting food/drink, rash) so may not exhibit change in a heterogeneously treated sample of patients, may require a longer duration of follow-up to exhibit change (arm/leg swelling, hair loss), or may be related to cognitive condition (headache, problems with concentration), which was not assessed in the Global Impression of Change items.

Strengths of this study include the diverse sample, reflecting a wide range of cancer types and treatment modalities, and enrichment for less common cancer types. The sample was also successfully enriched for patients with impaired PS (ECOG PS ≥ 2), enabling demonstration of the meaningfulness of PRO-CTCAE among those with substantial symptom burdens, as well as the feasibility of survey administration in debilitated patients. Moreover, participants were accrued at both academic and community sites across the United States, including rural and urban settings, and reflected a range of educational and racial backgrounds.

Several caveats should be considered. First, our study was conducted in an English-speaking US-residing patient population. Ongoing research is evaluating linguistic adaptations of PRO-CTCAE, and the measurement properties of both the English and other language versions in settings outside the United States.[31] Linguistic validation of a Spanish language translation of PRO-CTCAE is being reported elsewhere.[18] Second, we assessed reliability in a subset of 49 items; thus, future studies to examine the test-retest reliability of the remaining PRO-CTCAE items are warranted. Third, a small number of highly specific symptomatic AEs were uncommon in the study sample and received low endorsement rates, thus limiting our ability to evaluate their measurement properties. Specifically, 5 items reflecting 4 symptomatic AEs (nosebleeds; pain, swelling, and/or redness at site of drug injection or intravenous therapy; pain during vaginal sex; rash) did not exhibit a statistically significant and meaningful effect on at least 1 construct validity criterion. These items are being evaluated in other clinical trial contexts. Whereas the large number of items and anchors evaluated in this study raises the possibility of inflated type I error, in sensitivity analyses using more stringent significance thresholds, the majority of items retained statistical significance. Last, notwithstanding inclusion of participants with diverse cancer types in this study, results may not fully generalize to populations with rare tumor types. However, a prior cognitive interviewing study[16] affirms that PRO-CTCAE items were well understood by respondents with varying disease sites and receiving diverse anticancer treatments. Continued evaluation of PRO-CTCAE is currently under way in a variety of trial contexts to support the interpretability and value of patient reporting of symptomatic treatment-related toxic effects.

Conclusions

The CTCAE has historically enabled clinicians to describe the toxicity burden of cancer treatments using a consistent standard language allowing comparisons across trials. The value of patients' input in describing their own experiences is well recognized. Having a measurement system that integrates the patient perspective into AE reporting and that fosters consistency, transparency, and comparability across trials is similarly an important objective. The results of this validation study suggest that PRO-CTCAE can achieve its intended aim of integrating the patient experience into routine clinical trial AE reporting, thereby augmenting the capacity for informed decision making. In conclusion, this large-scale multicenter validation study in individuals undergoing active cancer therapy provides robust evidence for the validity, reliability, and responsiveness of items in the PRO-CTCAE library.

ARTICLE INFORMATION

Accepted for Publication: June 11, 2015.

Published Online: August 13, 2015. doi:10.1001/jamaoncol.2015.2639.

Author Affiliations: Department of Health Sciences Research, Mayo Clinic, Scottsdale, Arizona (Dueck); Department of Symptom Research, University of Texas MD Anderson Cancer Center, Houston (Mendoza, Cleeland); Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, Maryland (Mitchell, Castro, Clauser); Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill (Reeve, Bennett, Basch); Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York (Rogak, Basch); Department of Psychiatry and Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, New York (Atkinson, Li); Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville, Maryland (Denicoff, Minasian); Division of Cancer Prevention, National Cancer Institute, Rockville, Maryland (O'Mara); Department of Clinical Research, Cancer Program of Our Lady of the Lake and Mary Bird Perkins, Baton Rouge, Louisiana (Bryant); Gibbs Cancer Center and Research Institute, Spartanburg, South Carolina (Bearden); Helen F. Graham Cancer Center and Research Institute, Christiana Care Health System,

Newark, Delaware (Gillis); Center for Cancer Prevention and Treatment, St. Joseph Hospital of Orange, Orange, California (Harness); Helen and Harry Gray Cancer Center, Hartford Hospital, Hartford, Connecticut (Siegel); patient advocate and cancer survivor, Brooklyn, New York (Paul); Division of Population Sciences, Dana-Farber Cancer Institute, Boston, Massachusetts (Schrag); Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota (Sloan); Department of Medicine, Duke University Medical Center, Durham, North Carolina (Abernethy); Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, Georgia (Bruner).

Author Contributions: Dr Dueck had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Dueck, Mendoza, Mitchell, Reeve, Rogak, Atkinson, Denicoff, O'Mara, Clauser, Bryant, Paul, Cleeland, Schrag, Sloan, Abernethy, Bruner, Minasian, Basch.
Acquisition, analysis, or interpretation of data: Dueck, Mendoza, Mitchell, Reeve, Castro, Rogak, Atkinson, Bennett, Denicoff, O'Mara, Li, Bryant, Bearden, Gillis, Harness, Siegel, Paul, Schrag, Abernethy, Bruner, Basch.
Drafting of the manuscript: Dueck, Mitchell, Rogak, Atkinson, Bennett, Li, Bryant, Schrag, Sloan, Abernethy, Bruner, Basch.
Critical revision of the manuscript for important intellectual content: Dueck, Mendoza, Mitchell, Reeve, Castro, Rogak, Atkinson, Bennett, Denicoff, O'Mara, Clauser, Bearden, Gillis, Harness, Siegel, Paul, Cleeland, Schrag, Abernethy, Minasian, Basch.
Statistical analysis: Dueck, Mendoza, Mitchell, Rogak, Atkinson, Li, Sloan.
Obtained funding: Dueck, Castro, Abernethy.
Administrative, technical, or material support: Dueck, Mendoza, Mitchell, Castro, Rogak, Atkinson, Li, Clauser, Bryant, Gillis, Cleeland, Schrag, Bruner, Basch.
Study supervision: Dueck, Mitchell, Castro, Rogak, Siegel, Abernethy, Minasian, Basch.

Conflict of Interest Disclosures: Drs Dueck, Mendoza, and Reeve, Ms Rogak, and Drs Atkinson, Bennett, Li, Bryant, Bearden, Gillis, Harness, Siegel, Cleeland, Schrag, Sloan, Abernethy, Bruner, and Basch served as investigators or study managers under contract or subcontract from the National Cancer Institute to develop the PRO-CTCAE. No other disclosures are reported.

Funding/Support: This study was supported by contracts from the National Cancer Institute: HHSN261200800043C, HHSN261201000063C, and HHSN261200800001E.

Role of the Funder/Sponsor: National Cancer Institute scientific staff (Mitchell, Castro, Denicoff, O'Mara, Clauser, Minasian) participated in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: Additional National Cancer Institute PRO-CTCAE Study Group members are Narre Heon, BA; Mary Shaw, BA; Sean Ryan, MS; Liora P. Stark, MPH; and Laura Sit, MS (Memorial Sloan Kettering Cancer Center, New York, New York); Amy Thomassie, RN, BSN, CCRC (Cancer Program of Our Lady of the Lake and Mary Bird Perkins, Baton Rouge, Louisiana); Wendy Pettus, MS, and Lucy Gansauer, RN, MSN, OCN (Gibbs Cancer Center, Spartanburg, South Carolina); Barbara Marconi, RN; and Angela Steele-Tilton, MSN (Helen F. Graham Cancer Center and Research Institute, Christiana Care Health System, Newark, Delaware); Donna Malveaux (University of Texas M. D. Anderson Cancer Center, Houston); and Jennifer Wind, MA (Dana-Farber Cancer Institute, Boston, Massachusetts).

Additional Contributions: We thank the patients and clinicians who participated in this study. Gitana Davila and Kathy Alexander contributed study coordination, patient recruitment, and data management at the Center for Cancer Prevention and Treatment at St Joseph Hospital of Orange and Hartford Hospital–Helen and Harry Gray Cancer Center, respectively. Their institutions received funding to support their efforts. Neil Aaronson, PhD, provided methodological input on the EORTC QLQ-C30. He was not compensated for his contribution. The authors also wish to thank observers from the Food and Drug Administration who have provided valuable input during development of the PRO-CTCAE, including Ann Marie Trentacosti, MD; Virginia Kwitkowski, MS, RN, ACNP-BC; Laurie Burke, RPh, MPH (retired); Elektra Papadopoulos, MD, MPH; Ashley Slagle, PhD, MS; and Paul Kluetz, MD.

REFERENCES

1. National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. NIH publication 09-7473. Published May 29, 2009; Revised June 14, 2010. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed March 16, 2015.

2. Setser A. CTCAE v4.0: Frequently Asked Questions. http://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.01_2009-07-14_FAQ.doc. Accessed March 16, 2015.

3. Trotti A, Colevas AD, Setser A, Basch E. Patient-reported outcomes and the evolution of adverse event reporting in oncology. *J Clin Oncol*. 2007;25(32):5121-5127.

4. Atkinson TM, Li Y, Coffey CW, et al. Reliability of adverse symptom event reporting by clinicians. *Qual Life Res*. 2012;21(7):1159-1164.

5. Basch E. The missing voice of patients in drug-safety reporting. *N Engl J Med*. 2010;362(10):865-869.

6. Fromme EK, Eilers KM, Mori M, Hsieh YC, Beer TM. How accurate is clinician reporting of chemotherapy adverse effects? a comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. *J Clin Oncol*. 2004;22(17):3485-3490.

7. Pakhomov SV, Jacobsen SJ, Chute CG, Roger VL. Agreement between patient-reported symptoms and their documentation in the medical record. *Am J Manag Care*. 2008;14(8):530-539.

8. Basch E, Jia X, Heller G, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. *J Natl Cancer Inst*. 2009;101(23):1624-1632.

9. Quinten C, Maringwa J, Gotay CC, et al. Patient self-reports of symptoms and clinician ratings as predictors of overall cancer survival. *J Natl Cancer Inst*. 2011;103(24):1851-1858.

10. Meacham R, McEngart D, O'Gorman H, Wenzel K. Use and compliance with electronic patient reported outcomes within clinical drug trials. Paper presented at: 2008 ISPOR (International Society for Pharmacoeconomics and Outcomes Research) Annual International Meeting; May 3-7, 2008; Toronto, Ontario, Canada.

11. Judson TJ, Bennett AV, Rogak LJ, et al. Feasibility of long-term patient self-reporting of toxicities from home via the Internet during routine chemotherapy. *J Clin Oncol*. 2013;31(20):2580-2585.

12. Di Maio M, Gallo C, Leighl NB, et al. Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. *J Clin Oncol*. 2015;33(8):910-915.

13. Basch E, Iasonos A, McDonough T, et al. Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: results of a questionnaire-based study. *Lancet Oncol*. 2006;7(11):903-909.

14. Basch EM, Reeve BB, Mitchell SA, et al. Electronic toxicity monitoring and patient-reported outcomes. *Cancer J*. 2011;17(4):231-234.

15. Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *J Natl Cancer Inst*. 2014;106(9):dju244.

16. Hay JL, Atkinson TM, Reeve BB, et al; NCI PRO-CTCAE Study Group. Cognitive interviewing of the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *Qual Life Res*. 2014;23(1):257-269.

17. Agarwal H, Gulati M, Baumgartner P, et al. Web interface for the patient-reported version of the CTCAE. Paper presented at: NCI caBIG Annual Meeting; July 20-22, 2009; Washington, DC.

18. Arnold BJ, Mitchell SA, Lent L, et al. Linguistic validation of the Spanish translation of the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events. Paper presented at: International Society for Quality of Life Research 21st Annual Conference; October 15-18, 2014; Berlin, Germany.

19. Reeve BB, Mitchell SA, Dueck AC, et al. Recommended patient-reported core set of symptoms to measure in adult cancer treatment trials. *J Natl Cancer Inst*. 2014;106(7):dju129.

20. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376.

21. Gundy CM, Fayers PM, Groenvold M, et al. Comparing higher order models for the EORTC QLQ-C30. *Qual Life Res*. 2012;21(9):1607-1617.

22. Kieffer JM, Giesinger JM, Fayers P, et al. Replication and relative validity of the mental and physical higher order model of the EORTC QLQ-C30. Paper presented at: International Society for Quality of Life Research 21st Annual Conference; October 15-18, 2014; Berlin, Germany.

23. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. 1998;16(1):139-144.

24. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR; Clinical Significance Consensus Meeting Group. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc*. 2002;77(4):371-383.

25. Mendoza TR, Bennett AV, Mitchell SA, et al. Impact of recall period on the accuracy of selected items from the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Poster presented at: International Society for Quality of Life Research 21st Annual Conference; October 15-18, 2014; Berlin, Germany.

26. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, New Jersey: Lawrence Erlbaum Associates; 1988.

27. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull*. 1979; 86(2):420-428.

28. Nunnally JC, Berstein IH. *Psychometric Theory*. 3rd ed. New York: McGraw-Hill; 1994.

29. Jonckheere AR. A distribution-free k-sample test against ordered alternatives. *Biometrika*. 1954; 41:133-145.

30. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*. 1988; 75:800-802.

31. Kirsch M, Mitchell SA, Dobbels F, et al. Linguistic and content validation of a German-language PRO-CTCAE-based patient-reported outcomes instrument to evaluate the late effect symptom experience after allogeneic hematopoietic stem cell transplantation. *Eur J Oncol Nurs*. 2015;19(1):66-74.

Invited Commentary

PROceeding With the Patient-Reported Outcomes (PROs) Version of the Common Terminology Criteria for Adverse Events

Benjamin Movsas, MD

For more than 30 years, the standard process for reporting toxicities in clinical oncology trials has been via the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE). Overall, this system, which includes approximately 800 items, has served our field well, such that toxicities can be compared across clinical trials using a consistent language. Approximately 10% of the items represent symptoms (eg, fatigue, nausea) that are currently reported by clinicians. Prior studies, however, have shown that there is often a disconnect, with substantial discrepancies between patient and clinician reports of symptoms.[1] This begs the question: When it comes to reporting symptomatic adverse events, should the perspective of the patient or the clinician be primarily considered?

Related article

Some would argue that the clinician is most qualified to report symptomatic adverse events. After all, they have the professional training and background to place the patient's symptoms into the overall context of the disease process. However, prior studies have demonstrated that, compared with patients, clinicians tend to underreport the incidence and severity of patients' symptoms.[1] Quinten et al[2] provide evidence that the accuracy of clinician-based CTCAE reporting was enhanced by adding patient-reported outcomes (PROs) gleaned directly from patients. At a fundamental level, how can anyone know the patient's subjective experience better than the patient?

Others may contend that PROs are not scientifically rigorous because they are based on subjective reporting. However, many PRO instruments (such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [EORTC QLQ-C30] and the Functional Assessment of Cancer Therapy) have been rigorously tested for scientific validity and reliability.[1] The fact is that much PRO research is currently hypothesis driven and based on clinically meaningful changes using validated instruments.[1] On the other hand, the CTCAE itself was developed empirically by expert consensus but not evaluated for validity or reliability. Indeed, limitations of the CTCAE as a psychometric instrument to measure cancer symptom burden have previously been described.[2] In addition, PROs have often been shown to be more powerful than standard prognosticators for predicting survival in clinical oncology trials.[1] Both the Food and Drug Administration and NCI have adopted PROs in trials as the benchmark for measuring subjective experiences.

In light of these considerations, the NCI decided to develop a PRO measurement system as a companion to the CTCAE, called the PRO-CTCAE. In the article by Dueck and colleagues[3] in this issue of *JAMA Oncology*, the authors took on the daunting task of analyzing the construct validity, reliability, and responsiveness of the PRO-CTCAE system, which includes a library of 124 patient self-reporting items. This study included almost 1000 adult English-speaking patients with cancer undergoing chemotherapy and/or radiation therapy from 9 US cancer centers and community oncology practices. Patients completed the PRO-CTCAE items on tablet computers or by telephone at 2 clinic visits, 1 to 6 weeks apart, with a subset 1 day apart. The key comparators for validation were the Eastern Cooperative Oncology Group performance status and a validated quality-of-life (QOL) instrument (EORTC-QLQ-C30). Overall, they demonstrated favorable validity, reliability, and responsiveness of the PRO-CTCAE even in a rather diverse sample of patients with cancer, including some with impaired performance status. They also found significant correlations between the PRO-CTCAE item changes and the corresponding QOL scale changes.

Dueck and colleagues[3] deserve credit for validating such a large number of individual symptomatic toxicity items in such a diverse group of patients with cancer. Although this is an important first step, more work is needed. For example, less than 4% of the patients in this study underwent cancer surgery, so this group requires further study. As the authors point out, this study included only English-speaking, US-residing patients with cancer. Future studies will need to focus on linguistic and cultural adaptations of PRO-CTCAE both inside and outside the United States. The reliability data were limited to a subset of items, such that further analysis of the test reliability will be required. Practical issues will also need to be addressed regarding how PRO-CTCAE may affect administrative time, cost, and patient burden over time. Beyond logistic issues, the ultimate success of the PRO-CTCAE will depend on imparting its importance and relevance to patients, clinicians, and other stakeholders.

The PRO-CTCAE is exciting because it is a novel patient-centered approach to adverse event (AE) reporting. By incorporating PROs into the AE reporting system, it provides a direct and unbiased account of the patient experience that can guide future treatment recommendations. This can provide a more accurate summary of the patient's treatment experience, which will be relevant for labeling decisions and informing stakeholders and future users about the effects of treatment. As Basch and colleagues[4] have pointed out, a fundamental premise of the PRO-CTCAE project is that whereas clinicians have the ultimate responsibility for AE reporting regarding patient safety, patients are best able to describe

their own experiences. Thus, both patients and clinicians should play key roles in the reporting of symptomatic AEs.

In summary, the perspectives of the patients and the clinicians are indeed both essential in that they each provide valuable and complementary input, which, when integrated, provides a more robust appreciation of patients' symptoms. Clinicians contribute their professional experience to this evaluation, while patients directly communicate their subjective experiences.[4] The power of the PRO-CTCAE is that it intertwines the patient perspective directly into the AE reporting using a validated methodology that can facilitate informed decision making. In the future, the PRO-CTCAE may be used as a strategy to provide real-time information about patients' symptoms so that clinicians can enhance their communication with patients regarding symptom management. Importantly, randomized data have demonstrated that when inquiries are made regarding PROs in the clinic, not only did physician-patient communication significantly improve, but almost all patients also expressed interest in continuing this approach.[5] One thing is reasonably clear: when it comes to optimally understanding and appreciating the patient experience, our patients want us to "PRO"ceed with PROs.

ARTICLE INFORMATION

Author Affiliation: Department of Radiation Oncology, Henry Ford Hospital, Detroit, Michigan.

Corresponding Author: Benjamin Movsas, MD, Department of Radiation Oncology, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202 (bmovsas1@hfhs.org).

Published Online: August 13, 2015. doi:10.1001/jamaoncol.2015.2689.

Conflict of Interest Disclosures: Dr Movsas serves as cochair of the NCI NRG (National Surgical Adjuvant Breast and Bowel Project, Radiation Therapy Oncology Group, Gynecologic Oncology Group) Patient Centered Outcomes Research committee. His department receives research support from Varian, Inc, and Philips, Inc, not related to this Invited Commentary. No other disclosures are reported.

REFERENCES

1. Siddiqui F, Liu AK, Watkins-Bruner D, Movsas B. Patient-reported outcomes and survivorship in radiation oncology: overcoming the cons. *J Clin Oncol*. 2014;32(26):2920-2927.

2. Quinten C, Maringwa J, Gotay CC, et al. Patient self-reports of symptoms and clinician ratings as predictors of overall cancer survival. *J Natl Cancer Inst*. 2011;103(24):1851-1858.

3. Dueck AC, Mendoza TR, Mitchell SA, et al. Validity and reliability of the US National Cancer Institute's patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [published online August 13, 2015]. *JAMA Oncol*. doi:10.1001/jamaoncol.2015.2639.

4. Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *J Natl Cancer Inst*. 2014;106(9):dju244.

5. Detmar SB, Muller MJ, Schornagel JH, Wever LD, Aaronson NK. Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. *JAMA*. 2002;288(23):3027-3034.