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Feasibility Assessment of Patient Reporting of Symptomatic Adverse Events in Multicenter Cancer Clinical Trials

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Abstract

IMPORTANCE—In cancer clinical trials, symptomatic adverse events (AEs), such as nausea, are reported by investigators rather than by patients. There is increasing interest to collect symptomatic AE data via patient-reported outcome (PRO) questionnaires, but it is unclear whether it is feasible to implement this approach in multicenter trials.

OBJECTIVE—To examine whether patients are willing and able to report their symptomatic AEs in multicenter trials.

DESIGN, SETTING, AND PARTICIPANTS—A total of 361 consecutive patients enrolled in any 1 of 9 US multicenter cancer treatment trials were invited to self-report 13 common symptomatic AEs using a PRO adaptation of the National Cancer Institute's Common

Terminology Criteria for Adverse Events (CTCAE) via tablet computers at 5 successive clinic visits. Patient adherence was tracked with reasons for missed self-reports. Agreement with clinician AE reports was analyzed with weighted κ statistics. Patient and investigator perspectives were elicited by survey. The study was conducted from March 15, 2007, to August 11, 2011. Data analysis was performed from August 9, 2013, to March 21, 2014.

RESULTS—Of the 361 patients invited to participate, 285 individuals enrolled, with a median age of 57 years (range, 24–88), 202 (74.3%) female, 241 (85.5%) white, 73 (26.8%) with a high school education or less, and 176 (64.7%) who reported regular internet use (denominators varied owing to missing data). Across all patients and trials, there were 1280 visits during which patients had an opportunity to self-report (ie, patients were alive and enrolled in a treatment trial at the time of the visit). Self-reports were completed at 1202 visits (93.9% overall adherence). Adherence was highest at baseline and declined over time (visit 1, 100%; visit 2, 96%; visit 3, 95%; visit 4, 91%; and visit 5, 85%). Reasons for missing PROs included institutional errors in 27 of 48 (56.3%) of the cases (eg, staff forgetting to bring computers to patients at visits), patients feeling “too ill” in 8 (16.7%), patient refusal in 8 (16.7%), and internet connectivity problems in 5 (10.4%). Patient-investigator CTCAE agreement was moderate or worse for most symptoms (most $\kappa < 0.05$), with investigators reporting fewer AEs than patients across symptoms. Most patients believed that the system was easy to use (234 [93.2%]) and useful (230 [93.1%]), and investigators thought that the patient-reported AEs were useful (133 [94.3%]) and accurate (119 [83.2%]).

CONCLUSIONS AND RELEVANCE—Participants in multicenter cancer trials are willing and able to report their own symptomatic AEs at most clinic visits and report more AEs than investigators. This approach may improve the precision of AE reporting in cancer trials.

In cancer trials, it is standard practice for clinical investigators to report adverse events (AEs) 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 approximately 800 discrete AEs graded using a 5-point numerical grading system, with each grade anchored to discrete clinical criteria. Approximately 10% of CTCAE items represent symptoms (eg, nausea and sensory neuropathy) that, like nonsymptom AEs (eg, neutropenia and retinal detachment), have historically been reported by investigators and not by patients.[2] However, there is empirical evidence that investigators miss up to half of symptomatic AEs, that clinician interrater reliability for reporting symptomatic AEs is generally low, and that collection of this information directly from study participants as patient-reported outcomes (PROs) may improve the reliability and precision of symptomatic AE detection.[3–7]

Patient-reported outcomes are the standard used in clinical trials for measurement of health-related quality of life, physical functioning, and disease-related symptoms and are of growing interest in hospital quality assessment and comparative effectiveness research.[8–14] In 2005, the Food and Drug Administration published a draft guidance document (finalized in 2009) recommending the use of PROs whenever measuring concepts in clinical trials that are best evaluated from the patient’s perspective,[15] with a similar statement from the European Medicines Agency.[16]

Although PROs are increasingly used in these other contexts, they are not yet standard for AE reporting in clinical trials. The need for such an approach is particularly salient in oncology given that cancer therapies often carry substantial toxicity burdens that contribute to treatment nonadherence, discontinuation, dose reduction, and discomfort.[17–20] In a survey of more than 700 cancer clinical investigators and research staff, more than 90% believed that patient reporting of symptomatic AEs could improve data completeness, accuracy, meaningfulness, and actionability compared with the current standard approach based on physician reporting.[21] Single-center studies have demonstrated that collecting symptomatic AE information via the internet from patients receiving chemotherapy is feasible.[22,23]

Therefore, the NCI supported a national cooperative group study to assess the feasibility of asking patients to report their symptomatic AEs using plain language items based on CTCAE, version 3.0,[22,23] via a web-based platform[24] during participation in national multicenter NCI-sponsored cancer trials.

Methods

Patients and Sites

Patients enrolled in any 1 of 9 US national multicenter cancer trials supported by the NCI were eligible for simultaneous participation in this Cancer and Leukemia Group B (CALGB) correlative PRO feasibility study (CALGB 70501; clinicaltrials.gov, NCT00417040). The CALGB study is now part of the Alliance for Clinical Trials in Oncology. Patients could be registered to the PRO feasibility study at any time up until and including the second scheduled visit (cycle 2 of therapy). Included were 4 breast cancer trials,[25–28]1 colorectal cancer trial,[29] 2 lung cancer trials,[30,31]1 prostate cancer trial,[32] and 1 supportive care trial.[33] (eTable 1 in the Supplement provides details of each trial.) This PRO feasibility study was approved by the institutional review board at each accruing site (eAppendix in the Supplement), and all participants provided written informed consent that was separate from their consent to enroll in the associated treatment trial.

At each site, clinical research professionals (CRPs) underwent a standardized 20-minute, web-enabled teleconference before initiation of enrollment to learn how to use a secure online questionnaire system that has been usability tested and employed in multiple previous studies.[22–24] The CRPs were taught how to register patients into the system and administer symptom questionnaires to patients via wireless tablet computers. Sites were assessed for wireless internet connectivity in clinic waiting areas and the availability of computers, and wireless tablet computers and/or wireless connection hardware were provided to sites when needed.

Consecutive patients enrolled in the treatment trials were approached and invited to participate in the feasibility study if they were able to read and comprehend English and able to see a computer screen or were accompanied by a companion who could read a screen to the patient. Reasons for refusal to participate were systematically tracked. At the time of enrollment, site CRPs educated each participant to complete self-reported questions via tablet computers using a 10-minute standardized training session.

Questionnaire and Administration

The AE patient questionnaire included plain language items based on CTCAE, version 3.0 (eTables 2 and 3 in the Supplement). These items served as a basis for the NCI's recently developed PRO-CTCAE item library.[34,35] Specifically, patients completed questions about 13 symptomatic AEs, including anorexia (appetite loss), constipation, cough, diarrhea, dyspnea (shortness of breath), fatigue, hand or foot reaction or rash, mucositis (mouth sores), nausea, neuropathy, pain, vomiting, and watery eyes (eTable 2 in the Supplement). These questions were graded similarly to the clinician CTCAE using a 5-point ordinal scale for responses, with verbal descriptors of clinical anchors except with the use of lay terminology. For example, grade 3 anorexia is defined for clinicians in the CTCAE as "associated with significant weight loss or malnutrition (eg, inadequate oral caloric and/or fluid intake); IV [intravenous] fluids, tube feedings, or TPN [total parenteral nutrition] indicated" and grade 3 wording for the PRO adaptation is, "I am losing a lot of weight or I am malnourished, and I am taking in very little food or fluids (or I have needed to get IV fluids, tube feedings, or IV nutrition)."[22](p3555) To harmonize with the general approach to clinician CTCAE reporting, patient questionnaire instructions specified the following recall period: "Please answer the following questions to tell us the worst your symptoms have been since your last chemotherapy treatment. If you have not received chemotherapy, or your treatment has been held, please tell us the worst your symptoms have been since your last chemotherapy visit."[22](p3555) In the 9 clinical trials, treatment cycle length varied, and the recall periods for patient questionnaires therefore varied based on cycle length. Specifically, the cycle length was weekly in 1 trial, every 2 weeks in 1 trial, every 3 weeks in 5 trials, and every 4 weeks in 2 trials.

At each of 5 consecutive chemotherapy cycle clinic visits, a tablet computer was brought to participants in a private area of clinic waiting rooms to complete the questionnaire. The CRPs could provide technical assistance or explain terminology but could not provide assistance in symptom rating. At each visit, the CRPs printed reports showing the longitudinal trajectory of symptoms and added this information to medical records for nurses and oncologists. No specific instructions were given to clinicians regarding how to use these reports for clinical trial documentation or patient management. Simultaneously, clinicians reported the same symptomatic toxic effects using the standard CTCAE case report form utilized in cooperative group trials.

Adherence to self-reporting was systematically tracked, and site staff logged reasons for missed patient self-reports. At the third cycle visit (or off-study visit if before the third cycle), patients and clinical investigators completed a feedback survey with items regarding the ease of use and perceived value of the system.

Statistical Analysis

Participation rate was computed as the number of patients enrolled divided by the number approached to participate. Adherence was defined as the number of patients who completed the assessment divided by the total number who were alive and enrolled in the trial at each given visit. Criteria for determining feasibility were specified a priori as 80% or more participation and adherence rates. Descriptive statistics for patient symptom scores and

clinician grades included means (SDs) and frequencies of each response category. Agreement between patients and clinicians was assessed across all response categories using weighted κ statistics, with κ values ranging from 0.01 to 0.20 demarcating slight agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; and 0.61 or higher, substantial agreement.[36] Time to grade 2 or higher AEs was analyzed using the Kaplan-Meier[37] approach and is presented as a cumulative incidence curve separately based on patient and clinician reports. Feedback surveys were analyzed using descriptive statistics. Sample size was capped at 300 based on available funding and an assumption that this number would provide robust estimates of feasibility and preliminary estimates of agreement for patients who are representative of enrollees in National Clinical Trials Network trials. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center (SDC). Data quality was ensured by review of data by the Alliance SDC (A.C.D., D. Seisler, and P.J.A.) and by the study chairperson (E.B.) following Alliance SDC policies. Statistical analysis was conducted from August 9, 2013, to March 21, 2014, and was performed using SAS, version 9.3 (SAS Institute).

Results

This study enrolled patients between March 15, 2007, and August 11, 2011. Thirty-seven US sites completed CRP training and actively enrolled patients; 32 (86.5%) sites required tablet computers and 5 (13.5%) required wireless connectivity hardware to be set up in waiting rooms. A total of 361 patients were approached, with 313 agreeing to participate (86.7% participation rate), and 285 (91.1%) were alive and still receiving protocol-directed treatment at the time of study initiation. Among the 48 patients who refused participation, the most common reasons for nonparticipation were that the patient was not interested (29 [60.4%]) and was too anxious (6 [12.5%]); only 2 [4.2%] were too sick, 1 [2.1%] did not want to use a computer, 1 [2.1%] was too busy, 1 [2.1%] did not like research, and 8 [16.7%] did not specify a reason. More participants were women (202 [74.3%]) due to the included breast trials (4 of 9 included treatment trials), and most were white (241 [85.5%]); denominators differed for some variables because of missing data (Table 1). Within each trial, the patients enrolled in this PRO feasibility study were demographically similar to all other enrolled patients with respect to age, sex, and race. In some trials, the proportion of Hispanic/Latino patients was higher in the overall trial compared with those enrolled in this feasibility study because the PRO questionnaire was offered only in English.

During the study, there were 1280 scheduled visits at which participants were expected to complete a questionnaire (ie, visits at which patients were alive and enrolled in the associated trial). Of these, questionnaires were completed at 1202 visits (93.9% overall adherence rate). Adherence was best at baseline and successively declined over time (Figure 1). Rates exceeded the a priori feasibility threshold of 80% or higher adherence. Documented reasons for non adherence included institutional errors (eg, staff forgetting to bring tablets to patients at visits) in 27 of 48 (56.3%) cases, internet connectivity problems in 5 cases (10.4%), patients feeling too ill in 8 cases (16.7%), and patient refusal in 8 cases (16.7%).

Among the 285 participants, 222 (77.9%) had no missing assessments during the study and 63 (22.1%) had at least 1 missing assessment during the study. In comparing the linked treatment trial, age, sex, race, and ethnicity between the 63 patients with at least 1 missing assessment and the 222 patients without missing assessments, none reached statistical significance. Women were more likely to have no missing assessments, although this finding was not significant (81.0% vs 70.3% for men; $P = .07$).

Agreement in grade level between patient and clinician reports on toxic effects is reported in Table 2. Agreement based on weighted κ statistics was generally fair, with 6 of 13 symptomatic toxic AEs having weighted κ statistics between 0.21 and 0.40. Agreement was highest for vomiting (κ = 0.82) and lowest for hand-foot reaction or rash (κ = 0.03). Cumulative incidence of patient and clinician symptomatic toxic AEs of grade 2 or higher, shown in Figure 2 and the eFigure in the Supplement, demonstrate lower levels of reporting by clinicians compared with patients over time across all toxic AEs except hand-foot reaction or rash, where AE rates were low overall. The greatest levels of clinician underreporting compared with patients occurred for anorexia, fatigue, nausea, and pain.

Despite these discrepancies between patients and clinicians, most investigators reported in the feedback survey that they viewed and discussed patient self-reports at clinic visits and found the reports to be useful and accurate (Table 3). The survey was completed by 144 investigators at all 36 participating sites. The patient feedback survey, returned by 252 of 285 (88.4%) participants, found that most patients completed the reports themselves, viewed the system as easy to use and useful, and believed that the PRO approach improved discussions with clinicians (Table 3).

Discussion

To our knowledge, this is the first prospective study assessing patient self-reporting of symptomatic AEs in cancer multicenter clinical trials. Most patients were willing and able to self-report AEs at consecutive visits and found this process to be easy and useful. Similarly, most investigators found the patient reports to be useful and accurate, confirming a prior national survey in which more than 90% of investigators projected that patient reporting of AEs could improve meaningfulness and accuracy of AEs in clinical research.[8]

The most common reason for nonadherence was related to staff members; specifically, staff members forgot to bring tablets to patients in 56.3% of the documented cases. An additional 10.4% of missing self-reports were due to internet connectivity problems. These findings suggest that adherence rates could be boosted through standardized mechanisms to support staff and technology.

In subsequent National Clinical Trials Network studies integrating patient-reported AEs as a standard metric, centralized monitoring of adherence and automated reminders have been used to prompt staff to remember to collect data.[38–41] In addition, approaches have been used for between-visit reporting by patients via the internet or automated telephone systems to avoid reliance on site staff to bring computers to patients.[38,40] Strategies to optimize patient response rates will invariably improve as this approach to data collection becomes

more commonly used in trials. Nonetheless, the high participation and adherence rates observed within the present study suggest immediate feasibility of implementation.

In terms of internet connectivity problems and other technology limitations, there have been substantial technical and connectivity advances since this study opened; during the course of this study, we observed the frequency of such problems to fall substantially. Virtually all US oncology clinics now have high-speed internet in waiting areas, and most patients own a wireless device. We anticipate that the connectivity problems experienced in this study will be less of a barrier in the future, which is being assessed in follow-up work.[38,40]

Although most investigators reported viewing PROs at visits and believed that these were an accurate reflection of true patient status, there were discrepancies between patient and investigator grades, with investigators consistently reporting lower grades than patients. This paradoxical finding suggests either that investigators viewed PROs after documenting AEs or that investigators did not use the PROs to inform their AE documentation even though they found them valuable. In previous studies in which patients and clinicians reported side-by-side without viewing each other's documentation, there were similar discrepancies in grades[4,5,7]; in a more recent single-center phase 2 trial, there was more than 90% agreement between patients and investigators when investigators were compelled by a computer interface to review PROs before documenting AEs.[42] Ongoing National Clinical Trials Network trials are assessing the sharing of PRO AEs with investigators to assess whether investigator grades will better align with PROs.[38,40] Nonetheless, unfiltered patient reports provide a direct reflection of the patient's experience with symptomatic AEs, and the US Food and Drug Administration has advocated for this approach.[43]

Adverse events reported by patients but missed by clinicians reflect an area of the patient's experience that may warrant particular attention in the future, both to alleviate patient discomfort and identify currently undocumented safety signals. Such focus may be particularly salient for targeted therapies and immunotherapies that cause long-standing, low-grade toxic effects.

Limitations

There are several limitations of this study. Accrual was dependent on the 9 linked treatment trials, which increased at variable rates, leading to a relatively prolonged study period. Although we included a range of linked treatment trials in this study to allow for broad generalization of study results, the findings may not generalize to clinical trials that enroll patients with different characteristics (eg, higher rate of males or higher median age). The questionnaire was in English only, and future evaluations should include additional languages. Patient reporting was conducted only at clinic visits and not between visits when patients may experience important AEs. Ongoing trials are assessing between-visit reporting. A centralized backup reminder approach was not used, and this may be 1 reason that more than half of missing data were attributable to site staff forgetting to approach patients for self-reports at visits. A centralized reminder model is being assessed in ongoing work. Although the rates of reporting were high overall, they diminished over time. Work is in process to assess adherence rates with longer durations of selfreporting; in other settings, adherence has been shown to be durable over time.[44]

This study did not track time and effort by investigators, staff, or patients for conducting work for the PRO system, and this is a focus of ongoing evaluations in the National Clinical Trials Network. The recall period for patient questions in this study was “since your last chemotherapy,” which ranged from 1 to 4 weeks in the 9 trials. Ongoing work assessing the PRO-CTCAE has used standardized recall periods in clinical trials, and there is evidence that recall periods up to 4 weeks correlate with daily reporting, although shorter recall periods may be more precise.[45,46]

The questionnaire and software used in this study were precursors to the NCI’s PRO-CTCAE item library and software platform, which is now available and should be considered the standard approach for assessment of patient-reported AEs in oncology.[34,35] The conceptual framework for the study reported herein as well as the study team’s experiences through-out the conduct of this study informed the development of the PRO-CTCAE, but the data were not formally available until this analysis. The patient questions included in this study mirror the structure of CTCAE items with lay terminology, whereas the development of PRO-CTCAE items was based on established methods for designing PRO measures.

Performance status data were not universally collected in the linked clinical trials and therefore were not available as a baseline variable. It is possible that adherence rates would be lower in a population with worse or declining performance status, although adherence rates remained high over time in this study and are comparable to those of single-center PRO studies that included patients with substantial performance status limitations at baseline.[22,42,44] Most participants (74.3%) were women due to the composition of linked clinical trials and so may not be representative of trials with a different distribution by sex, although no significant differences in adherence rates were discernable between men and women in this study.

Conclusions

This study demonstrates the feasibility of patient self-reporting of AEs in multicenter cancer clinical trials, elucidates areas for further refinement, and paves the way for a more patient-centered and accurate approach to symptomatic AE reporting in cancer clinical research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

Is it feasible to collect patient-reported symptomatic adverse events in large multicenter oncology clinical trials?

Findings

Among 285 patients enrolled in 9 US multicenter cancer treatment trials, symptomatic adverse events were successfully self-reported by paients at 93.9% of expected times. Most patients believed that the system was easy to use and useful, and investigators thought that the patient-reported adverse event data were useful and accurate.

Meaning

Participants in multicenter cancer trials can report their own symptomatic adverse events, which may improve the efficiency and accuracy of safety monitoring in clinical research.

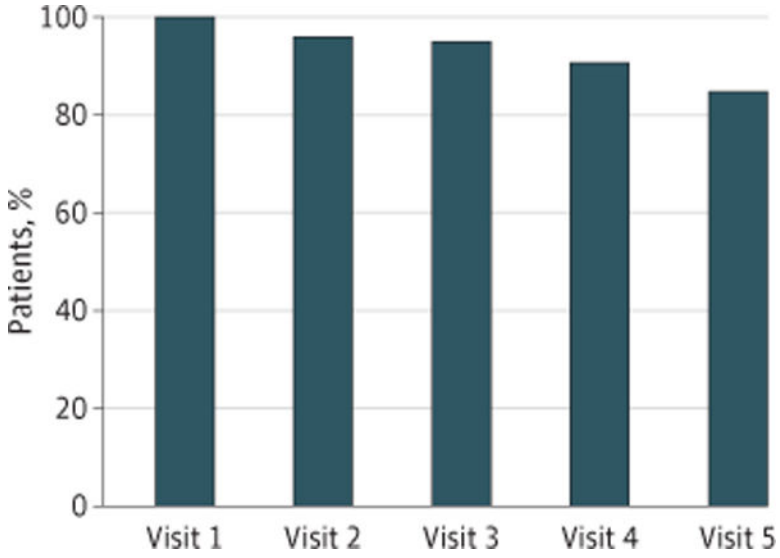

Figure 1. Proportion of Clinical Trial Participants Adhering to Symptomatic Adverse Event Reporting at Successive Clinic Visits

At each predetermined scheduled clinic visit, the proportion of remaining participants who successfully self-reported their own adverse events electronically was tabulated.

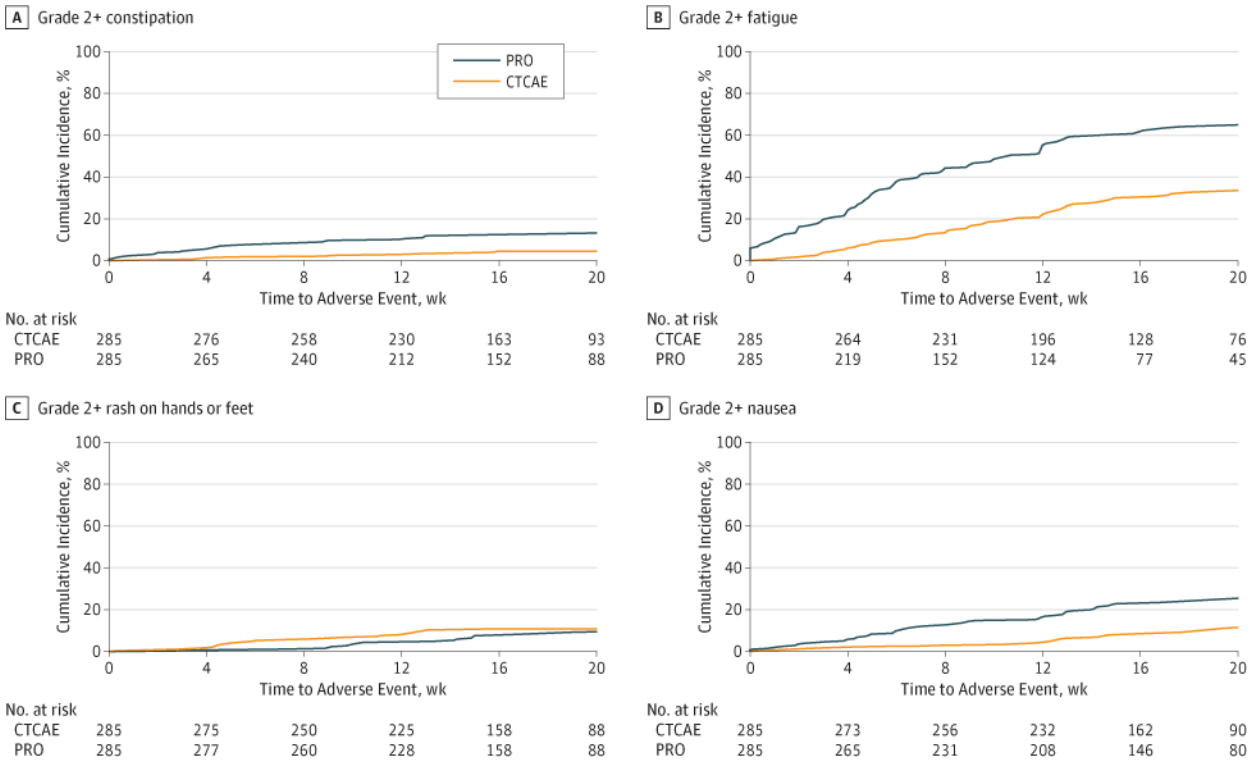

Figure 2. Cumulative Incidence of Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 or Higher Patient- and Clinician-Reported Adverse Events

Incidence aggregated from 9 US multicenter clinical trials for constipation (A), fatigue (B), hand or foot rash (C), and nausea (D). The eFigure in the Supplement provides the incidence for all 13 adverse events. PRO indicates patient-reported outcome.

Table 1

Characteristics of the 285 Participants

Characteristic	No. (%)
Age, median (range), y	57 (24–88)
Sex	
Female	202 (74.3)
Missing/NR[a]	13
Race[b]	
White	241 (85.5)
Black	31 (11.0)
Asian	8(2.8)
American Indian/Alaska native	2 (0.7)
Missing/NR[a]	3
Ethnicity	
Hispanic/Latino	7(2.9)
Missing/NR[a]	47
Cancer treatment trial type	
Breast cancer	151 (53.0)
Colorectal cancer	16 (5.6)
Lung cancer	10 (3.5)
Prostate cancer	14 (4.9)
Supportive care	94 (33.0)
Computer at home	
Yes	222 (82.5)
Missing/NR[a]	16
Frequency of internet use	
Regularly	176 (64.7)
Occasionally/rarely	57 (21.0)
Never	39 (14.3)
Missing/NR[a]	13
Highest educational level	
High school or less	73 (26.8)
Some college/college degree	152 (55.9)
Graduate degree	47 (17.3)
Missing/NR[a]	13

Abbreviation: NR, not reported.

[a]Data were not reported for clinical trials in which these individuals were enrolled. Missing data were removed from the denominator for proportions in each demographic category.

[b] Based on self-report. Percentages sum to greater than 100% owing to rounding.

Table 2

Levels of Agreement Between Symptomatic Toxic Effect Grades as Reported by Patients vs Clinicians

Symptomatic Toxic Effect	Weighted κ (95% CI)[a]
Anorexia	0.22 (0.07 to 0.37)
Constipation	0.39 (0.24 to 0.54)
Cough	0.36 (0.16 to 0.56)
Diarrhea	0.63 (0.49 to 0.76)
Dyspnea	0.32 (0.13 to 0.50)
Fatigue	0.33 (0.17 to 0.49)
Hand or foot rash	0.03 (−0.05 to 0.11)
Mouth sores	0.44 (0.25 to 0.63)
Nausea	0.65 (0.49 to 0.81)
Neuropathy	0.48 (0.33 to 0.64)
Pain	0.61 (0.48 to 0.74)
Vomiting	0.82 (0.62 to 1.00)
Watery eyes	0.23 (0.00 to 0.45)

[a]Weighted κ values ranging from 0.01 to 0.20 demarcate slight agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; and 0.61 or higher, substantial agreement.

Table 3

Clinical Investigator and Patient Feedback Surveys

Survey Item	Respondents, No. (%)
Clinical Investigator Feedback[a]	
Patient-reported symptomatic toxicities	
Were reviewed at visits	131/143 (91.6)
Were discussed with patients at visits	110/144 (76.4)
Are useful for monitoring toxicities	133/141 (94.3)
Could be a source of research-grade data	120/143 (83.9)
Were an accurate reflection of patient clinical status	119/143 (83.2)
Impression of relationship between adverse event grade severities reported by patients vs clinicians	
They are generally the same	63/143 (44.1)
Patients generally grade more severe than clinicians	50/143 (35.0)
Patients generally grade less severe than clinicians	13/143 (9.1)
Don’t know	17/143 (11.9)
Patient Feedback[b]	
Person who entered symptom grades	
Myself	220/250 (88.0)
Relative or friend	5/250 (2.0)
Professional caregiver	16/250 (6.4)
Other	9/250 (3.6)
The patient adverse event reporting system	
Was easy to use	234/251 (93.2)
Was useful	230/247 (93.1)
Improved discussions with mydoctor/nurse	211/247 (85.4)

[a]Overall, there were 144 clinical investigator respondents across 37 sites, but not all investigators responded to all questions; therefore, the denominator for each question varies with missing responses subtracted.

[b]Overall, there were 252 patient respondents of 285 study participants, but not all patients responded to all questions; therefore, the denominator for each question varies with missing responses subtracted.