

Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial

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Published online ahead of print at www.jco.org on December 7, 2015.

Supported by the National Cancer Institute and a grant from the Society of Memorial Sloan Kettering.

The National Cancer Institute and the Steps for Breath Fund of Memorial Sloan Kettering Cancer Center did not play any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT00578006.

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0732-183X/16/3406w-557w/\$20.00

DOI: 10.1200/JCO.2015.63.0830

ABSTRACT

Purpose

There is growing interest to enhance symptom monitoring during routine cancer care using patient-reported outcomes, but evidence of impact on clinical outcomes is limited.

Methods

We randomly assigned patients receiving routine outpatient chemotherapy for advanced solid tumors at Memorial Sloan Kettering Cancer Center to report 12 common symptoms via tablet computers or to receive usual care consisting of symptom monitoring at the discretion of clinicians. Those with home computers received weekly e-mail prompts to report between visits. Treating physicians received symptom printouts at visits, and nurses received e-mail alerts when participants reported severe or worsening symptoms. The primary outcome was change in health-related quality of life (HRQL) at 6 months compared with baseline, measured by the EuroQol EQ-5D Index. Secondary endpoints included emergency room (ER) visits, hospitalizations, and survival.

Results

Among 766 patients allocated, HRQL improved among more participants in the intervention group than usual care (34% v 18%) and worsened among fewer (38% v 53%; $P < .001$). Overall, mean HRQL declined by less in the intervention group than usual care (1.4- v 7.1-point drop; $P < .001$). Patients receiving intervention were less frequently admitted to the ER (34% v 41%; $P = .02$) or hospitalized (45% v 49%; $P = .08$) and remained on chemotherapy longer (mean, 8.2 v 6.3 months; $P = .002$). Although 75% of the intervention group was alive at 1 year, 69% with usual care survived the year ($P = .05$), with differences also seen in quality-adjusted survival (mean of 8.7 v 8.0 months; $P = .004$). Benefits were greater for participants lacking prior computer experience. Most patients receiving intervention (63%) reported severe symptoms during the study. Nurses frequently initiated clinical actions in response to e-mail alerts.

Conclusion

Clinical benefits were associated with symptom self-reporting during cancer care.

J Clin Oncol 34:557-565. © 2015 by American Society of Clinical Oncology

INTRODUCTION

Symptoms are common among patients receiving treatment of advanced cancers^{1,2} and often go undetected.³⁻⁶ Systematic collection of symptom information using patient-reported outcome (PRO) standardized questionnaires has been suggested as an approach to improve symptom control.^{7,8} Several web-based systems exist^{9,10} and have been shown to prompt clinicians to intensify symptom management,¹¹⁻¹³ to improve symptom control,^{11,13-15} and to enhance patient-

clinician communication, patient satisfaction, and well-being.¹⁶⁻²² Most patients are willing and able to self-report via the web, even close to the end of life.²³

The effects of symptom self-reporting on clinical outcomes are not established, leaving open the question of whether the benefits of systems to elicit PRO self-reports outweigh their added cost and burden.^{9,16,17} Symptoms precipitate emergency room (ER) visits and hospital admissions,²⁴ but it is not known if such visits are potentially avoidable through improved prospective monitoring. Several symptoms are associated with

worse survival in advanced cancer and lead to functional impairment and deconditioning.²⁵ Therefore, improved symptom control may improve survival. To address these questions, we conducted a single-center randomized controlled trial to test whether systematic web-based collection of patient-reported symptoms during chemotherapy treatment, with automated alerts to clinicians for severe or worsening symptoms, improves health-related quality of life (HRQL) as well as survival, quality-adjusted survival, ER use, and hospitalization.

METHODS

Trial Design and Participants

Patients initiating chemotherapy at Memorial Sloan Kettering Cancer Center (MSK) in New York for metastatic breast, genitourinary, gynecologic, or lung cancers were enrolled in a nonblinded, randomized, controlled trial of web-based self-reporting of symptoms, compared with usual care. The study protocol was approved by the MSK institutional review board and registered on ClinicalTrials.gov (NCT00578006).

Patients were eligible if they planned to receive chemotherapy at MSK and could read English. Patients were ineligible if they were participating in an investigational treatment, because such studies stipulate structured symptom reporting. The included tumor types were selected because they represent a spectrum of symptoms related to cancer and treatment; metastatic disease was specified because treatment is often continuous and symptoms are common.¹ All participants provided written informed consent. Randomization was conducted by the institutional Biostatistics Service via a computer system using randomly permuted blocks. Participants remained on study until discontinuation of cancer treatment, voluntary withdrawal, or death.

Preplanned Subgroups

Before randomization, participants were assigned to one of two subgroups based on level of prior computer and e-mail use. Those with regular access to a computer and e-mail use at least weekly were assigned to a computer-experienced subgroup; the remainder were assigned to a computer-inexperienced subgroup. This approach was based on evidence that patients with computer experience are more receptive to electronic self-reporting than those with less computer experience.²⁶ The patients in each subgroup were independently allocated to self-reporting versus usual care (1:1 in the computer-experienced subgroup and enriched at 2:1 in the computer-inexperienced subgroup, to enable an assessment of the logistics of obtaining PROs in this group as a part of a parallel feasibility study).

Intervention

Self-reporting was conducted via STAR (Symptom Tracking and Reporting), a web-based interface previously established as easy to use for patients with cancer with high symptom burdens.^{20,27-29} STAR includes questions adapted for patient use from the National Cancer Institute's Common Terminology Criteria for Adverse Events,^{26,27} pertaining to 12 common symptoms experienced during chemotherapy^{1,30}: appetite loss, constipation, cough, diarrhea, dyspnea, dysuria, fatigue, hot flashes, nausea, pain, neuropathy, and vomiting. These symptoms are graded on a five-point scale from 0 (not present) to 4 (disabling) based on clinical criteria.³¹ STAR did not allow skipped questions or free-text responses.

At enrollment, nonclinical study staff trained participants to use STAR and facilitated completion of a baseline self-report. At subsequent medical oncology or infusion suite visits, study staff invited participants to self-report either via wireless touchscreen tablet computers or free-standing computer kiosks. Participants in the computer-inexperienced subgroup were asked to self-report using STAR only at clinic visits. Participants in the computer-experienced subgroup were given remote access to STAR, with a weekly e-mail reminder encouraging but not requiring a between-visit report.

STAR triggered e-mail alerts to nurses whenever a patient-reported symptom worsened by ≥ 2 points or reached an absolute grade ≥ 3 . The system informed participants that e-mails are not generally monitored after business hours, and participants were therefore encouraged to call the office at such times for symptoms of concern. A report tracking participants' symptoms^{20,23,26} was printed at each clinic visit for both the nurse and treating oncologist. No specific guidance was provided to clinicians about what actions to take in response to alerts or printed symptom profiles.

Usual Care

Usual care for both the computer-experienced and computer-inexperienced subgroups consisted of the standard procedure at MSK for monitoring and documenting symptoms, which is typical of medical oncology practice and was identical for both subgroups.^{5,20} Symptoms are discussed and documented in the medical record during clinical encounters between patients and their oncologists. Patients are encouraged to initiate telephone contact between visits for concerning symptoms.

Outcome Measures

The primary outcome was change in HRQL at 6 months from baseline, measured via the EuroQol EQ-5D Index.³² The EQ-5D Index is a five-item questionnaire (measuring mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that produces a composite score between 0 and 1 (multiplied by 100 to yield a result between 0-100) representing general health status, normalized for the US population.^{33,34} Lower scores represent worse HRQL. A score change of 6 points on the 0 to 100 scale is considered clinically meaningful in US cancer populations.³⁵ The EQ-5D was administered via paper at clinic visits every 12 ± 4 weeks throughout study participation, with an understanding that in the routine care setting, clinic visit intervals vary between patients.

Survival at 1 year was tabulated based on medical records and Social Security Death Index data. Quality-adjusted survival was evaluated by multiplying EQ-5D scores by survival time for each patient.³⁶ Time to first ER visit and time to first hospitalization at MSK were based on admissions data in the medical record. Time receiving active cancer treatment was abstracted from medical charts. The number of nursing calls to patients was tabulated based on nursing logs in the medical record.

Adherence with STAR self-reporting was assessed by calculating the proportion of participants completing questionnaires at each successive visit. For computer-inexperienced participants to be considered adherent at a given visit, a self-report must have been completed at the time of that visit. For computer-experienced participants to be adherent at a given visit, a STAR report had to be completed remotely within 72 hours. Nurses used a standardized form to record if and what clinical actions were taken in response to e-mail alerts.

Statistical Analysis

The study was designed to accommodate combined and separate analyses of the computer-experienced and computer-inexperienced subgroups. Based on prior work,²⁸ it was projected that 30% to 40% of participants would fall in the inexperienced category. The experienced subgroup was randomized 1:1 and the inexperienced was randomized 2:1, to facilitate focus on the feasibility of obtaining PROs in this group. The study planned to enroll until 225 patients were allocated within the smaller inexperienced subgroup (150 assigned to STAR and 75 to usual care). With 225 participants in the inexperienced subgroup, there was 80% power to detect an effect size of 0.40 in mean EQ-5D index change from baseline between arms using a *t* test with a two-sided α of 0.05.

For the primary quality-of-life analysis, EQ-5D index scores for participants in each study arm were calculated at 6 months and compared with baseline scores, excluding those who did not complete any post-baseline EQ-5D questionnaire and using the last postbaseline observation carried forward when available for patients without 6-month data. The proportion of patients in each arm who experienced improved,

unchanged, or worsened scores from baseline was compared using Fisher's exact test. This analysis was conducted both for any level of change from baseline and for a 6-point change from baseline, which is considered as clinically meaningful.³⁴ Mean score changes from baseline were compared using two group *t* tests. A multivariable linear regression model, with change score as the dependent variable, adjusted for covariates including age, sex, cancer type, race, and education level. Multiple sensitivity imputation analyses were conducted including last observation carried forward but including baseline observations for patients with no postbaseline EQ-5D score, no observations carried forward, minimum observation values carried forward, average observation values carried forward, and last observation carried forward but assigning an EQ-5D value of zero if death occurred before 6 months. For each method, analyses were conducted separately for the whole group and for the subgroups based on computer experience.

For ER and hospitalization endpoints, cumulative incidence functions were calculated with death treated as a competing event.³⁷ Competing risk regression was used to model risk with and without adjustment for baseline covariates.

Comparisons of the percentage of patients alive at 1 year were made using logistic regression, adjusting for baseline covariates, because complete survival data were available for all patients. For the quality-adjusted survival analysis, participants' average EQ-5D scores were multiplied by survival times for each EQ-5D reporting interval during the initial year of enrollment; these values were summed to yield a total number of quality-adjusted life months for that patient during that year.³⁵ Participants with missing baseline EQ-5D scores were excluded. Mean quality-adjusted life months were compared between arms in each cohort, using two group *t* tests. A multivariable linear regression model was used to adjust for the baseline covariates in Table 1.

Two-sided *P* values of less than .05 were considered to indicate statistical significance.

RESULTS

Baseline Characteristics

Between September 14, 2007 and January 6, 2011, 1,007 subjects were identified as potentially eligible and approached to participate. Of these, 154 were found to be ineligible, and 87 declined. The remaining 766 subjects were enrolled and randomly assigned, including 227 computer-inexperienced and 539 computer-experienced participants (Fig 1). Mean time on study was 7.4 months and median time was 3.7 months (range, 0.25 to 49), with a mean of 16 clinic visits per patient (range, 1 to 114).

Baseline characteristics were balanced between randomization arms in both the computer-experienced and -inexperienced subgroups (Table 1). Computer-inexperienced participants were significantly older, more often men, more often black, and less educated than computer-experienced participants (all *P* < .001).

Quality of Life

HRQL scores improved by any amount from baseline to 6 months among more participants in the STAR arm than in the usual care arm (34% v 18%) and worsened among fewer (38% v 53%; *P* < .001; Fig 2; Data Supplement). Similarly, more participants in the STAR arm experienced an improvement in HRQL by the previously established clinically meaningful score change threshold of ≥ 6 points³⁴ compared with usual care (21% v 11%), and fewer experienced a ≥ 6 -point worsening (28% v

Table 1. Baseline Characteristics of the Participants

| Characteristic | All Patients (N = 766) | | Computer-Experienced Subgroup (n = 539) | | Computer-Inexperienced Subgroup (n = 227)* | |
|---------------------------------------|------------------------|----------------------|---|----------------------|--|---------------------|
| | STAR (n = 441) | Usual Care (n = 325) | STAR (n = 286) | Usual Care (n = 253) | STAR (n = 155) | Usual Care (n = 72) |
| Age, median (range), years | 61 (30-91) | 62 (26-88) | 59 (30-85) | 60 (26-88) | 67 (38-91) | 67 (44-86) |
| Female sex | 257 (58) | 187 (58) | 184 (64) | 152 (60) | 73 (47) | 35 (49) |
| Race | | | | | | |
| White | 377 (86) | 283 (87) | 253 (89) | 230 (91) | 124 (80) | 53 (74) |
| Black† | 43 (10) | 24 (7) | 20 (7) | 10 (4) | 23 (15) | 14 (19) |
| Asian | 21 (5) | 18 (6) | 13 (5) | 13 (5) | 8 (5) | 5 (7) |
| Cancer type | | | | | | |
| Genitourinary | 143 (32) | 102 (31) | 78 (27) | 77 (30) | 65 (42) | 25 (35) |
| Gynecologic | 97 (22) | 80 (25) | 67 (23) | 66 (26) | 30 (19) | 14 (19) |
| Breast | 89 (20) | 54 (17) | 72 (25) | 47 (19) | 17 (11) | 7 (10) |
| Lung | 112 (25) | 89 (27) | 69 (24) | 63 (25) | 43 (28) | 26 (36) |
| Education | | | | | | |
| High school or less | 106 (24) | 64 (20) | 46 (16) | 36 (14) | 60 (39) | 28 (39) |
| College | 205 (47) | 155 (48) | 143 (50) | 125 (49) | 62 (40) | 30 (42) |
| Graduate degree | 130 (30) | 106 (33) | 97 (34) | 92 (36) | 33 (21) | 14 (19) |
| HRQL‡ | | | | | | |
| Mean | 0.85 | 0.84 | 0.86 | 0.85 | 0.82 | 0.84 |
| Range | 0.27-1.0 | 0.20-1.00 | 0.33-1.00 | 0.22-1.00 | 0.27-1.00 | 0.20-1.00 |
| Days since initiation of chemotherapy | | | | | | |
| Mean | 46 | 40 | 44 | 41 | 51 | 39 |
| Range | 0-1,025 | 0-840 | 0-511 | 0-840 | 0-1,025 | 0-427 |

NOTE. Data presented as No. (%) unless otherwise noted. No significant differences between study arms were seen for any of the baseline characteristics in the study population overall or within either of the subgroups (all *P* > .3).

Abbreviations: HRQL, health related quality of life; STAR, Symptom Tracking and Reporting web-based self-reporting system (study intervention).

*Randomized 2:1 in this subgroup.

†Includes four patients categorized as "other" at enrollment and determined by chart review to have black race.

‡HRQL measured via the EuroQoL EQ-5D questionnaire.

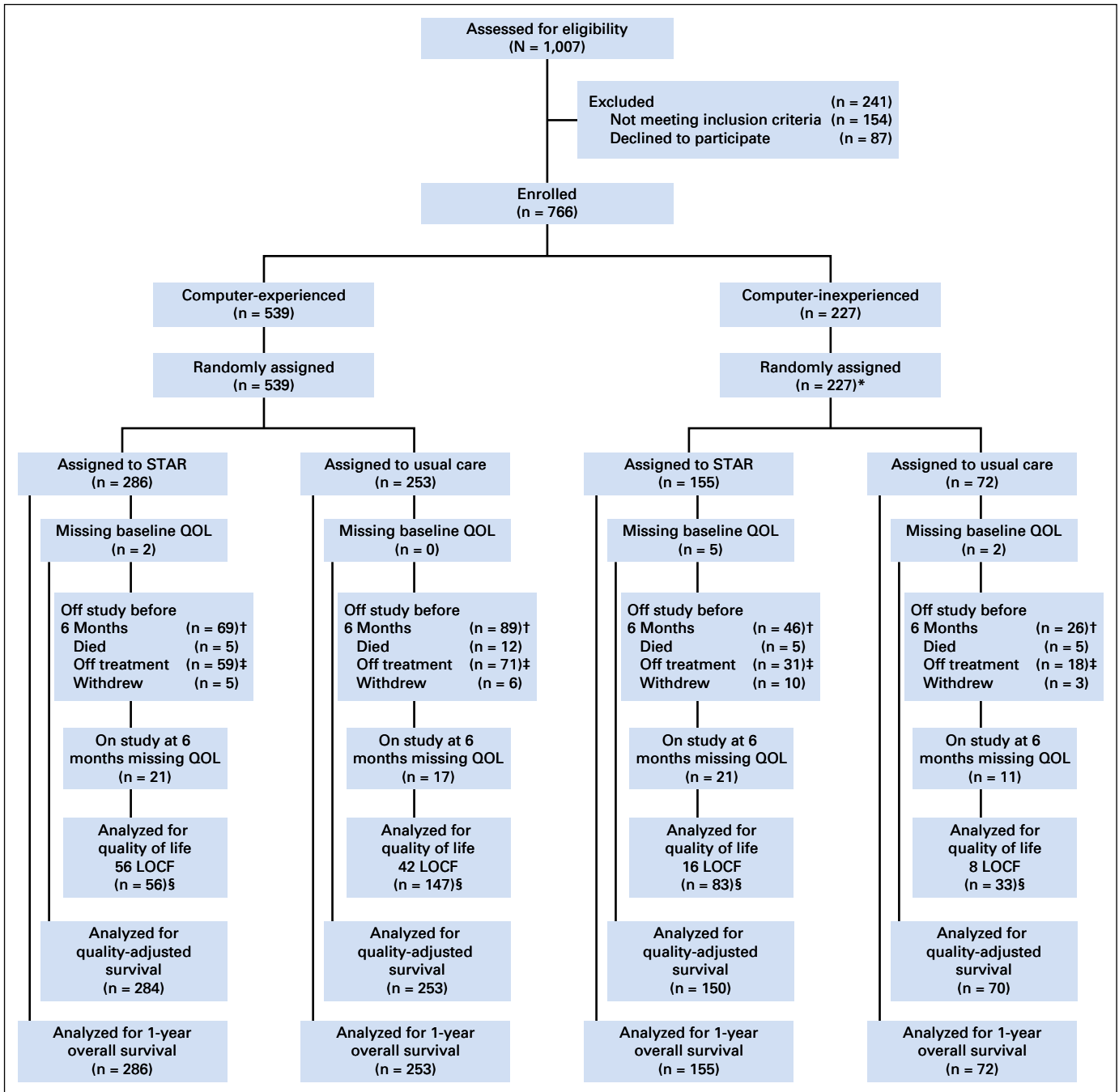


Fig 1. CONSORT diagram. *Computer-inexperienced patients were allocated 2:1, Symptom Tracking and Reporting web-based self-reporting system (STAR) to usual care. †Participants went off study before reporting postbaseline quality of life (QOL). ‡Participants discontinued chemotherapy treatment before 6 months. §Last observation carried forward (LOCF) for participants who went off study before 6 months but reported a prior postbaseline QOL.

37%; $P = .001$). Mean HRQL scores declined by less in the intervention arm compared with usual care (1.4- v 7.1-point drop; $P < .001$; Table 2). Although effect sizes were the same in the two subgroups (0.38), results were statistically significant in the computer-experienced subgroup ($P < .001$) but did not reach statistical significance in the relatively smaller computer-inexperienced subgroup ($P = .06$). Notably, 230 patients (30% of participants) died or discontinued cancer treatment before completing a follow-up HRQL questionnaire. In a sensitivity analysis that included

these individuals by carrying forward their baseline HRQL values, results were similar; results were also robust across multiple additional sensitivity analyses (Data Supplement). In an analysis of the EQ-5D's subdomains, three were statistically significantly better with STAR compared with usual care at 6 months compared with baseline, including Mobility ($P = .02$), Self-Care ($P = .01$), and Anxiety/Depression ($P = .01$), but did not reach significance for Pain/Discomfort ($P = .05$) or Usual Activities ($P = .09$).

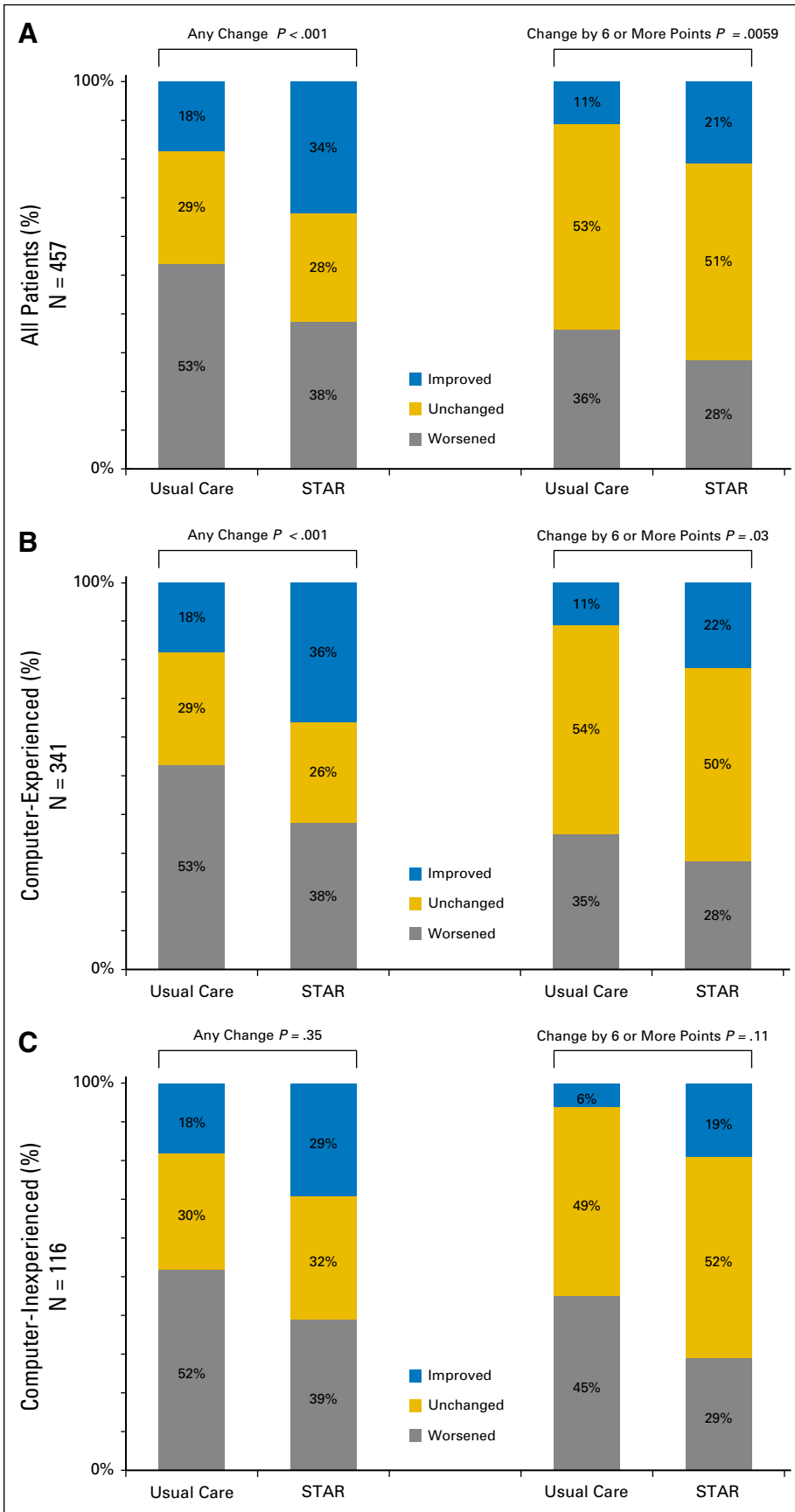


Fig 2. Proportion of patients with health-related quality-of-life changes at 6 months compared with baseline. The proportion of patients in each study arm was tabulated for which EuroQoL EQ-5D Index scores improved, remained unchanged, or worsened by any amount at 6 months compared with baseline. This analysis was repeated using a threshold for change of six or more points, an amount considered to be clinically meaningful in US cancer populations. Results are shown (A) for all participants, and separately for (B) the computer-experienced subgroup, and (C) the computer-inexperienced subgroup. Analyses included only patients with available baseline and postbaseline EQ-5D scores. *P* values were calculated using Fisher's exact test comparing study arms based on the three categories of comparison (improved, unchanged, worsened). STAR, Symptom Tracking and Reporting web-based self-reporting system (study intervention).

Table 2. Mean Quality-of-Life Changes From Baseline at 6 Months

| Patients | N* | STAR (n = 277) | Usual Care (n = 180) | P (Univariable)† | P (Multivariable)† | Effect Size |
|---------------------------------------|-----|----------------------|----------------------|------------------|--------------------|-------------|
| Evaluable patients* | 457 | | | | | |
| EQ-5D at baseline | | 86.2 (84.7 to 87.7) | 86.6 (84.7 to 88.5) | | | |
| EQ-5D at 6 months | | 84.8 (83.2 to 86.4) | 79.5 (76.7 to 82.2) | | | |
| Point drop from baseline | | 1.4 (0.4 to 3.1) | 7.1 (4.8 to 9.5) | | | |
| Difference in point drop between arms | | | 5.7 | <.001 | <.001 | 0.37 |
| Subgroup analysis | | | | | | |
| Computer-inexperienced subgroup* | 116 | | | | | |
| EQ-5D at baseline | | 83.6 (80.2 to 86.9) | 86.9 (81.9 to 91.9) | | | |
| EQ-5D at 6 months | | 81.8 (78.2 to 85.3) | 78.6 (71.2 to 86.0) | | | |
| Point drop from baseline | | 1.8 (to 2.1 to 5.7) | 8.3 (3.6 to 13.1) | | | |
| Difference in point drop between arms | | | 6.5 | .06 | .11 | 0.38 |
| Computer-experienced subgroup* | 341 | | | | | |
| EQ-5D at baseline | | 87.3 (85.7 to 88.6) | 86.5 (84.5 to 88.6) | | | |
| EQ-5D at 6 months | | 86.1 (84.3 to 87.8) | 79.7 (76.7 to 82.7) | | | |
| Point drop from baseline | | 1.2 (0.7 to 3.1) | 6.9 (4.2 to 9.5) | | | |
| Difference in point drop between arms | | | 5.7 | <.001 | <.001 | 0.38 |

NOTE. Data presented as mean (95% CI) unless otherwise noted.

Abbreviations: STAR, Symptom Tracking and Reporting web-based self-reporting system; EQ-5D, EuroQoL EQ-5D quality of life questionnaire.

*Patients without postbaseline EQ-5D scores were not included in the primary health-related quality of life analysis but were included in the sensitivity analysis with similar results.

†P values for between-arm comparisons. Multivariable analyses controlled for age, sex, cancer type, race, and education level. For overall analyses, subgroup assignment (computer experienced or computer inexperienced) was also included as a covariate.

ER Visits, Hospitalization, Cancer Treatment

Fewer participants in the STAR arm visited the ER compared with usual care (34% v 41% at 1 year; P = .02; Fig 3). These differences appeared more pronounced in the computer-inexperienced subgroup (34% v 56%; P = .02) than in the computer-experienced subgroup (34% v 36%; P = .16). A similar trend was seen in the proportion of patients hospitalized at 1 year for the overall study population (45% v 49%; P = .08), again more pronounced and significant in the computer-inexperienced subgroup (44% v 63%; P = .003) but not in the computer-experienced subgroup (46% v 45%; P = .75; Data Supplement). Patients in the STAR arm received active chemotherapy treatment for significantly longer than usual care during the study, with a mean of 8.2 months (range, 0 to 49 months) versus 6.3 months (range, 0 to 41 months), respectively (P = .002), and a median of 4.1 months versus 3.5 months, respectively (P = .002).

Overall and Quality-Adjusted Survival

At 1 year, 69% of patients were alive in the usual-care arm compared with 75% with STAR, a difference of 6% (P = .05; Table 3). This difference was more pronounced among computer-inexperienced participants (60% vs. 74%; P = .02), with a trend seen among computer-experienced participants (71% v 76%; P = .45). Significant differences in quality-adjusted survival were observed during this 1-year period for all patients (mean of 8.0 v 8.7 months; P = .004) and were statistically significant in both subgroups.

Symptom Reporting and Nurse Responses to E-mail Alerts

On average, 73% of participants assigned to the intervention arm completed a self-report at any given clinic visit (Data Supplement). A total of 84,212 individual symptoms were self-reported during the study. Among these, 1,431 or 1.7% were severe

or disabling (grade 3 or 4), reported by 277 of the 441 (63%) intervention arm participants. The most common severe or disabling patient-reported symptoms were fatigue, pain, anorexia, dyspnea, neuropathy, and nausea. Nursing interventions taken in direct response to e-mail alerts included telephone counseling about symptom management (in response to 77% of alerts), supportive medication initiation/change (12%), referral to the ER/hospital (8%), chemotherapy dose modification (2%), and imaging/test orders (2%). No difference in the number of nursing calls to patients during participation was detected, with a mean of 12.8 in the STAR group vs. 12.9 in the control group (P = .93).

DISCUSSION

For adults receiving outpatient chemotherapy for advanced cancer at a large specialty cancer center, web-based symptom reporting with automated clinician e-mail alerts resulted in better HRQL, fewer ER visits, fewer hospitalizations, a longer duration of palliative chemotherapy, and superior quality-adjusted survival.

Although the vast majority of patient-reported symptoms were grade 1 or 2 (mild to moderate), more than 1,400 were grade 3 or 4 (severe to disabling). In response to e-mail alerts for severe or worsening symptoms, nurses performed direct interventions primarily composed of telephone counseling, medication changes, and ER or hospital referral. Clinical actions may also have been taken in response to symptom reports delivered to clinicians at each office visit including responses to mild/moderate symptoms, although these were not systematically tracked and may be a useful focus of future research.

Prior studies have explored mechanisms by which patient reporting of symptoms may confer clinical benefits, with findings including increased rates of symptom discussions between patients and clinicians,^{11,18,19} intensified symptom management by

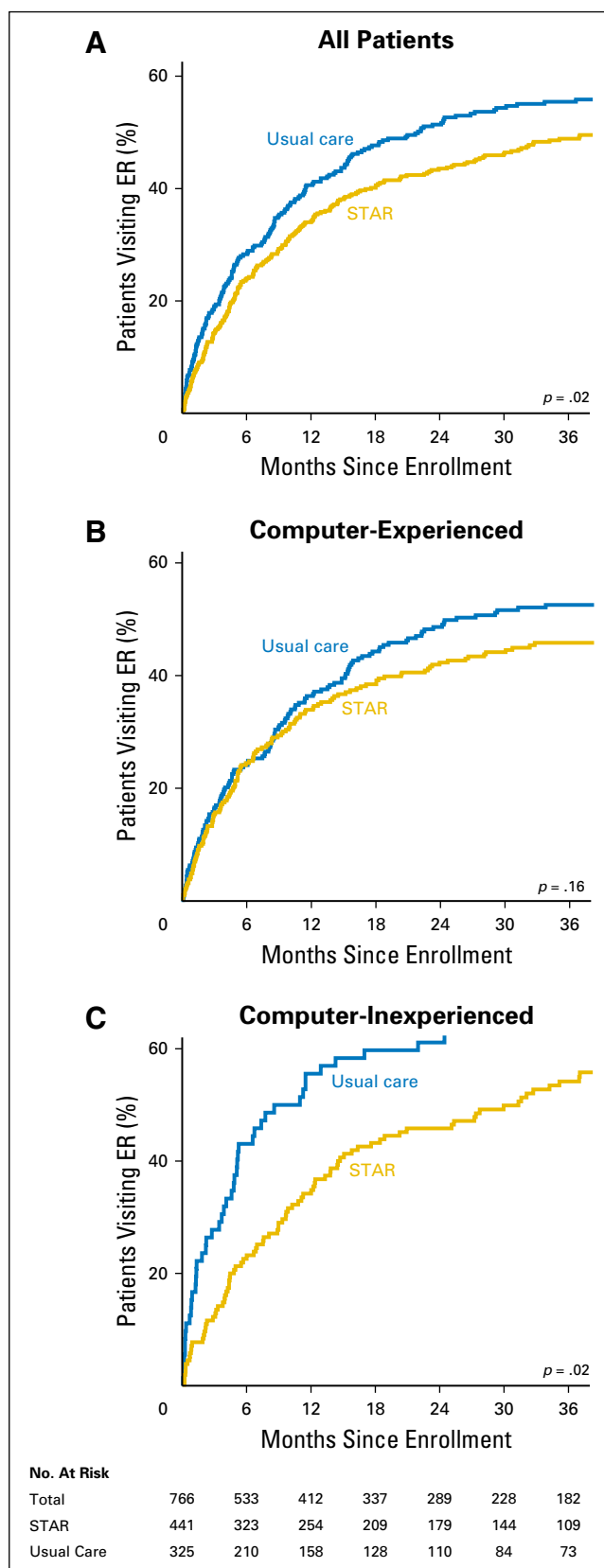


Fig 3. Cumulative incidence of emergency room (ER) visits. The incidence of patients visiting the ER is shown, with death as a competing event. (A) All patients; (B) computer-experienced patients; (C) computer-inexperienced patients. STAR, Symptom Tracking and Reporting web-based self-reporting system (study intervention).

clinicians in response to patient reports,¹¹⁻¹³ and improved symptom control when patient reports are shared with clinicians.^{11-14,18} As such, systematic patient reporting appears to enhance clinician awareness and can augment existing mechanisms for symptom management during routine oncology care. Conversely, when undetected in the absence of patient self-reporting, symptoms may continue to worsen and cause serious complications, lead to hospital visits, limit the ability to safely deliver chemotherapy, and diminish outcomes, as observed in this study.

This randomized trial should be interpreted in the context of three key limitations. First, it was conducted at a single, urban tertiary care cancer center limiting generalizability. However, inclusion of a computer-inexperienced subgroup, with 39% having no education beyond high school, suggests its applicability to diverse US cancer populations. The study included only English speakers; future assessments should include additional languages and nontext interfaces, such as interactive voice response. ER and hospital admissions regardless of primary site were tracked based on the institution's electronic medical record system. However, some admissions to outside institutions may not have been recorded.

Second, we chose to use the EQ-5D assessment of overall HRQL rather than more granular questionnaires that evaluate particular symptoms in detail. We selected this approach to avoid conflating the intervention with the outcome metric and to enable calculation of quality-adjusted survival. As a result, we have limited information about which symptoms were best addressed by symptom reporting. Despite the generic nature of the EQ-5D measure, significant and clinically meaningful differences were observed between study arms.

Third, substantial numbers of participants did not have 6-month HRQL data available because they had died or discontinued treatment. The survival and utilization endpoints would not be affected by these missing data, and HRQL results were similar in multiple sensitivity analyses. Moreover, missing HRQL would be more likely expected to attenuate detection of potential benefits of PRO reporting because of informative censoring of scores when patients died or discontinued treatment earlier in the usual care arm who otherwise might have reported low HRQL scores.³⁸ Nonetheless, earlier or more frequent systematic outcomes data collection is warranted for future assessments. The study design did not anticipate the observed level of attrition in the accrual plan.

Some benefits appeared greater for computer-inexperienced patients, who were overall older, frailer, and more symptomatic than computer-experienced patients. Participants lacking computer experience may have less-developed health communication skills and thereby benefit more from a structured program for eliciting symptoms. Future work is warranted to discern which patient populations may benefit most from this type of health communication intervention.

A formal cost-utility analysis was not performed. Resource use was relatively modest and included software development, server space and maintenance, eight tablet computers, and time spent by patients and clinicians to report and review symptoms and to respond when they were severe or worsening. The software did not provide recommendations to patients or clinicians about management of detected symptoms, which could be added in future systems.

Table 3. Overall and Quality-Adjusted Survival at 12 Months

| Patients | N | STAR (95% CI) | Usual Care (95% CI) | P (Univariable)* | P (Multivariable)* |
|--|------|---------------------|---------------------|------------------|--------------------|
| Overall survival, % alive at 1 year | | | | | |
| All patients | 766 | 75.1 (70.7 to 79.0) | 68.6 (63.2 to 73.6) | .03 | .05 |
| Subgroup analysis, % alive at 1 year | | | | | |
| Computer inexperienced | 227 | 74.2 (66.6 to 80.9) | 59.7 (47.5 to 71.1) | .03 | .02 |
| Computer experienced | 539 | 75.5 (70.1 to 80.4) | 71.1 (65.1 to 76.7) | .25 | .45 |
| Quality-adjusted 12-month survival, months | | | | | |
| All patients | 757† | 8.7 (8.3 to 9.0) | 8.0 (7.6 to 8.4) | .002 | .004 |
| Subgroup analysis, months | | | | | |
| Computer inexperienced | 220† | 8.3 (7.8 to 8.8) | 7.2 (6.3 to 8.2) | .03 | .02 |
| Computer experienced | 537† | 8.8 (8.5 to 9.2) | 8.2 (7.7 to 8.6) | .02 | .046 |

Abbreviation: STAR, Symptom Tracking and Reporting web-based self-reporting system (study intervention).

*P values for between-arm comparisons. Multivariable analyses controlled for age, sex, cancer type, race, and education level. For overall analyses, subgroup assignment (computer experienced or computer inexperienced) was also included as a covariate.

†Participants with missing baseline health-related quality of life scores not included in quality-adjusted survival analysis.

In the context of a changing health care delivery system where both population management and patient centeredness are prioritized, symptom self-reporting engages patients as active participants and may improve the experience, efficiency, and outcomes of care. Given the favorable outcomes we have demonstrated with a simple prototype, further work to refine optimal strategies for engaging both patients and clinicians in harnessing technology to improve care should be a priority.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

REFERENCES

1. Reilly CM, Bruner DW, Mitchell SA, et al: A literature synthesis of symptom prevalence and severity in persons receiving active cancer treatment. *Support Care Cancer* 21:1525-1550, 2013
2. Henry DH, Viswanathan HN, Elkin EP, Traina S, Wade S, Cella D: Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S. *Support Care Cancer* 2008;16:791-801
3. Fromme EK, Eilers KM, Mori M, et al: 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* 22:3485-3490, 2004
4. Laugsand EA, Sprangers MA, Bjordal K, et al: Health care providers underestimate symptom intensities of cancer patients: A multicenter European study. *Health Qual Life Outcomes* 8:104, 2010
5. Atkinson TM, Li Y, Coffey CW, et al: Reliability of adverse symptom event reporting by clinicians. *Qual Life Res* 21:1159-1164, 2012
6. Fisch MJ, Lee JW, Weiss M, et al: Prospective, observational study of pain and analgesic prescribing in medical oncology outpatients with breast, colorectal, lung, or prostate cancer. *J Clin Oncol* 30:1980-1988, 2012
7. Snyder CF, Aaronson NK, Choucair AK, et al: Implementing patient-reported outcomes assessment

in clinical practice: A review of the options and considerations. *Qual Life Res* 21:1305-1314, 2012

8. Fung CH, Hays RD: Prospects and challenges in using patient-reported outcomes in clinical practice. *Qual Life Res* 17:1297-1302, 2008

9. Jensen RE, Snyder CF, Abernethy AP, et al: Review of electronic patient-reported outcome systems used in cancer clinical care. *J Oncol Pract* 10:e215-e222, 2014

10. Bennett AV, Jensen RE, Basch E: Electronic patient-reported outcome systems in oncology clinical practice. *CA Cancer J Clin* 62:337-347, 2012

11. Seow H, Sussman J, Martelli-Reid L, et al: Do high symptom scores trigger clinical actions? An audit after implementing electronic symptom screening. *J Oncol Pract* 8:e142-e148, 2012

12. Santana MJ, Feeny D, Johnson JA, et al: Assessing the use of health-related quality of life measures in the routine clinical care of lung-transplant patients. *Qual Life Res* 19:371-379, 2010

13. Kroenke K, Krebs EE, Wu J, et al: Telecare collaborative management of chronic pain in primary care: A randomized clinical trial. *JAMA* 312:240-248, 2014

14. Cleeland CS, Wang XS, Shi Q, et al: Automated symptom alerts reduce postoperative symptom severity after cancer surgery: A randomized controlled clinical trial. *J Clin Oncol* 29:994-1000, 2011

15. Gilbert JE, Howell D, King S, et al: Quality improvement in cancer symptom assessment and

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16. Valderas JM, Kotzeva A, Espallargues M, et al: The impact of measuring patient-reported outcomes in clinical practice: A systematic review of the literature. *Qual Life Res* 17:179-193, 2008

17. Chen J, Ou L, Hollis SJ: A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. *BMC Health Serv Res* 13:211, 2013

18. Kotronoulas G, Kearney N, Maguire R, et al: What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. *J Clin Oncol* 32:1480-1501, 2014

19. Detmar SB, Muller MJ, Schornagel JH, et al: Health-related quality-of-life assessments and patient-physician communication: A randomized controlled trial. *JAMA* 288:3027-3034, 2002

20. Basch E, Artz D, Dulko D, et al: Patient online self-reporting of toxicity symptoms during chemotherapy. *J Clin Oncol* 23:3552-3561, 2005

21. Velikova G, Booth L, Smith AB, et al: Measuring quality of life in routine oncology practice improves communication and patient well-being: A randomized controlled trial. *J Clin Oncol* 22:714-724, 2004

- 22.** Berry DL, Blumenstein BA, Halpenny B, et al: Enhancing patient-provider communication with the electronic self-report assessment for cancer: A randomized trial. *J Clin Oncol* 29:1029-1035, 2011
- 23.** 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* 31:2580-2585, 2013
- 24.** Mayer DK, Travers D, Wyss A, et al: Why do patients with cancer visit emergency departments? Results of a 2008 population study in North Carolina. *J Clin Oncol* 29:2683-2688, 2011
- 25.** Trajkovic-Vidakovic M, de Graeff A, Voest EE, et al: Symptoms tell it all: A systematic review of the value of symptom assessment to predict survival in advanced cancer patients. *Crit Rev Oncol Hematol* 84:130-148, 2012
- 26.** Basch EM, Thaler HT, Shi W, et al: Use of information resources by patients with cancer and their companions. *Cancer* 100:2476-2483, 2004
- 27.** Basch E, Iasonos A, Barz A, et al: Long-term toxicity monitoring via electronic patient-reported outcomes in patients receiving chemotherapy. *J Clin Oncol* 25:5374-5380, 2007
- 28.** Basch E, Jia X, Heller G, et al: Adverse symptom event reporting by patients vs clinicians: Relationships with clinical outcomes. *J Natl Cancer Inst* 101:1624-1632, 2009
- 29.** Basch E, Artz D, Iasonos A, et al: Evaluation of an online platform for cancer patient self-reporting of chemotherapy toxicities. *J Am Med Inform Assoc* 14:264-268, 2007
- 30.** Basch E, Abernethy AP, Mullins CD, et al: Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness research in adult oncology. *J Clin Oncol* 30:4249-4255, 2012
- 31.** National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services: Common Terminology Criteria for Adverse Events (CTCAE). http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf
- 32.** EuroQol Group: EuroQol—A new facility for the measurement of health-related quality of life. *Health Policy* 16:199-208, 1990
- 33.** Agency for Healthcare Research and Quality. U.S. Valuation of the EuroQol EQ-5D Health States. January 2012. <http://archive.ahrq.gov/professionals/clinicians-providers/resources/rice/EQ5Dproj.html>
- 34.** Sullivan PW, Ghushchyan V: Mapping the EQ-5D index from the SF-12: US general population preferences in a nationally representative sample. *Med Decis Making* 26:401-409, 2006
- 35.** Pickard AS, Neary MP, Cella D: Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes* 5:70, 2007
- 36.** Zhao H, Tsiatis AA: A consistent estimator for the distribution of quality adjusted survival time. *Biometrika* 84:339-348, 1997
- 37.** Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 16:1141-1154, 1988
- 38.** Ratcliffe J, Young T, Longworth L, et al: An assessment of the impact of informative dropout and nonresponse in measuring health-related quality of life using the EuroQol (EQ-5D) descriptive system. *Value Health* 8:53-58, 2005



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

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Speakers' Bureau: WebMD

Research Funding: BIND Biosciences, Exelixis, Janssen Pharmaceuticals, Medivation, Janssen Diagnostics, Innocrin Pharmaceuticals

Travel, Accommodations, Expenses: Janssen Pharmaceuticals, Sanofi, Endocyte, AstraZeneca, Genentech, Bristol-Myers Squibb, Pfizer, Takeda Pharmaceuticals, Ferring, WIRB-Copernicus Group, Astellas Pharma, BIND Therapeutics, Celgene, Astellas Pharma

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Acknowledgment

We thank the study participants and the many physicians and nurses who reviewed and responded to symptom reports; Kai Lin, Charmaine Pun, and Kevin Shannon for technical work developing the STAR patient self-report web platform; Hojin Yang for statistical programming support; and Colin Begg, PhD, for programmatic support of this study. We also thank this study's clinical research associates and data managers, Narre Heon, Dawn Lavene, Sean Ryan, Mary Shaw, and Liora Stark. Peter Bach, MD, Bryce Reeve, PhD, and Thomas Stinchcombe, MD, provided valuable feedback on the manuscript.