nature medicine

Article

https://doi.org/10.1038/s41591-025-03507-y

Symptom monitoring with electronic patient-reported outcomes during cancer treatment: final results of the PRO-TECT cluster-randomized trial

Received: 10 June 2024

Accepted: 13 January 2025

Published online: 07 February 2025

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Symptoms are often underdetected during cancer treatment. To determine if symptom monitoring with electronic patient-reported outcomes (PROs) improves clinical outcomes, we conducted a cluster-randomized trial in which 52 oncology practices were assigned to PRO or usual care. At PRO practices, patients with metastatic cancer were invited to complete weekly symptom surveys. Severe or worsening symptoms generated alerts to the care team. The primary outcome was overall survival, and secondary outcomes included emergency visits, time to deterioration of physical function, symptoms, health-related quality of life (HRQL) and patient satisfaction with PRO. Among 1,191 enrolled patients, there was no difference in survival (hazard ratio (HR) 0.99 (95% confidence interval (CI), 0.83–1.17); $P = 0.86$). Time to first emergency visit was significantly prolonged with PRO compared to usual care (HR 0.84 ((95% CI, 0.71–0.98); $P = 0.03$), with a 6.1% reduction in the cumulative incidence of emergency visits and fewer mean visits at 12 months with PRO (1.02 versus 1.30; $P < 0.001$). Benefits also significantly favored PRO for delayed deterioration of physical function (median 12.6 versus 8.5 months, HR 0.73; $P = 0.002$), symptoms (12.7 versus 9.9, HR 0.69; $P < 0.001$) and HRQL (15.6 versus 12.2, HR 0.72; $P = 0.001$), which remained significant when considering deaths in analyses. Most patients felt that PRO improved discussions with the care team (77.0% (188/244)), made them feel more in control of their care (84.0% (205/244)) and would recommend it to other patients (91.4% (223/244)). Patients completed 91.5% (20,565/22,486) of expected weekly symptom surveys. These findings demonstrate that symptom monitoring with PRO meaningfully improves clinical outcomes, the patient experience and utilization of services and should be included as a standard part of quality cancer clinical care. Future studies of PRO in clinical care should focus on these outcomes rather than mortality as primary endpoints. ClinicalTrials.gov registration: NCT03249090

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Patients with cancer frequently experience symptoms that cause functional impairments, worsened quality of life and hospitalizations[1–3], yet these symptoms often go undetected by care teams during cancer treatment[4–6], presenting an opportunity to improve outcomes by optimizing symptom detection and prompting interventions by clinicians.

Software systems that administer electronic patient-reported outcome (PRO) surveys during cancer treatment offer a solution for improving the detection of symptoms during cancer treatment[7,8]. These systems typically involve a digital interface through which patients can self-report symptoms on a regular basis, such as weekly, via an electronic survey using a computer, smartphone or automated telephone system. Severe or worsening symptoms trigger alert notifications to the care team electronically, enabling the team to react and manage concerning symptoms in near-real time. Graphs or tables showing longitudinal symptom trajectories can be viewed by the care team at patients' clinic visits to guide discussions and care.

Prior prospective trials and observational studies have reported benefits of implementing such electronic PRO symptom monitoring systems on quality of life outcomes, emergency department and hospital utilization and in some cases survival among patients receiving cancer treatment[8–14]. For example, the single-center STAR randomized trial among 766 patients with metastatic cancers treated in New York found statistically significant benefits associated with electronic PRO symptom monitoring compared to usual care, including 15% fewer patients experiencing health-related quality of life (HRQL) deterioration at 6 months, and a 7% decrease in emergency visits[10]. A subsequent analysis of data from that trial found a statistically significant overall survival benefit of 5.2 months[11]. A Canadian population-based observational study among more than 128,000 patients with cancer who either participated or did not participate in PRO symptom monitoring similarly found a statistically significant 8% reduction in emergency visits and a 14% reduction in hospitalizations associated with PRO[13]. The French randomized CAPRI trial combined electronic PRO symptom monitoring with navigation services and found a statistically significant improvement in quality of life, reduced hospitalizations and decreased treatment-related adverse events[14].

To complement this body of evidence with a national trial in the United States, and modeled on the approach used in the STAR study, a multicenter cluster-randomized trial, PRO-TECT (Alliance AFT-39; NCT03249090), was designed and conducted in 52 community oncology practices to evaluate the real-world impact of electronic PRO symptom monitoring on clinical outcomes compared to usual care. Secondary outcomes of this trial were previously published including quality of life and patient experience[15,16], demonstrating clinically meaningful and statistically significant benefits of PRO symptom monitoring, and high levels of patient and clinician satisfaction with using PRO symptom monitoring. Outcomes that were not yet available at that time are now mature to report, including overall survival, emergency department visits and time to deterioration of quality of life adjusted for survival.

At the time the PRO-TECT trial was designed, overall survival was selected as a primary outcome because of its common inclusion as a key endpoint in cancer drug clinical research. However, over time, the importance of outcomes that measure how patients feel and function has risen in importance in cancer research and value-based cancer care delivery. Therefore, if this trial were to be redesigned today, a primary outcome related to quality of life would be more appropriate, such as physical function, symptom control or HRQL. These outcomes were included in this trial as prespecified secondary outcomes, and they are particularly important for understanding whether the intervention yields meaningful benefits for patients. A purpose of the intervention is to improve symptom detection and management by care teams, which can best be assessed through measurement of impact on quality of life outcomes and utilization of emergency services.

A cluster-randomized approach was selected for this trial with the intention to avoid theoretical potential spillover of enhanced attention to symptom management among control group patients. However, if this trial were to be redesigned today, patient-level randomization would be preferable, because spillover to nonintervention patients is unlikely to occur in the setting of busy practices, and it represents a smaller threat to trial conduct compared to the risk of introducing baseline imbalances between groups due to practice-level knowledge of study arm allocation.

PRO-TECT was designed to evaluate the impact of electronic PROs for symptom monitoring on meaningful outcomes in the context of contemporary clinical cancer care delivery and to be generalizable across all cancer types and treatments.

Results

Participant disposition

As shown in Fig. 1, 52 community oncology practices were included and randomized, with 26 assigned to PRO and 26 assigned to usual care control. No randomized practices were excluded from the trial. At these practices, between 31 October 2017 and 23 March 2020, 1,444 patients were approached and 1,191 were enrolled (593 PRO, 598 usual care control), with follow-up through 23 March 2022 (Fig. 1). The median age of participants was 63 years (range, 28–93), 694 (58.3%) were female, 925 (79.5%) were White, 468 (39.4%) had a high school education or less, 201 (16.9%) had 'never' used the internet and 317 (26.6%) were treated at rural practice locations (Table 1). Baseline imbalances were observed between groups in the proportion of patients receiving third-line or higher cancer therapy, and in the proportion of patients who had received a palliative care consultation, indicating more advanced disease and less supportive care among patients in the PRO group. Specifically, there were 380 (31.9%) patients overall receiving third-line or higher cancer therapy at baseline (211 (35.6%) in the PRO group and 169 (28.3%) in the control group; 7.3% difference between groups) and 145 (12.2%) patients overall who had received a palliative care consultation (51 (8.6%) in the PRO group and 94 (15.7%) in the control group; 7.1% difference between groups).

Among patients in the PRO group, 378/593 (63.7%) chose to use the web-based interface, whereas 215/593 (36.3%) chose to use the automated telephone interface throughout trial participation. Patients who chose to use the automated telephone system rather than web were more often rural (32.1% versus 22.5%), older (median age 65.0 versus 62.0) and had less educational attainment (54.0% versus 27.0% high school or less). In terms of patient adherence with symptom reporting, patients in the PRO group completed 20,565/22,486 (91.5%) of expected weekly PRO surveys, with similar completion rates for web-based reporting (92.6%) and automated telephone-based reporting (89.9%)[15].

Overall survival

All participating patients were included in the analysis in the primary outcome of overall survival (Fig. 1). There was no statistically significant difference between study groups in this outcome at 2 years with an HR (HR) of 0.99 (95% confidence interval (CI) 0.83–1.17, $P = 0.86$). The unadjusted Kaplan-Meier estimated survival at 2 years was 42.0% (95% CI, 38.2%–46.2%) for the PRO intervention group and 43.5% (95% CI, 39.7%–47.6%) for usual care control (Fig. 2).

A sensitivity analysis was conducted using a 12-month follow-up time point as a cutoff, with an HR of 1.02 (95% CI, 0.83–1.24, $P = 0.86$). An additional sensitivity landmark analysis starting at 1-month post-baseline, including all patients who were alive at 1 month, showed an HR of 1.06 (95% CI, 0.86–1.30).

Within subgroups of patients defined by baseline covariates, no meaningful difference in overall survival was observed between randomization groups (Extended Data Fig. 1). The observed intracluster correlation coefficient for overall survival was 0.02.

Emergency department visits

The secondary outcome, time to first emergency department visit, was statistically significantly prolonged (improved) in the PRO intervention

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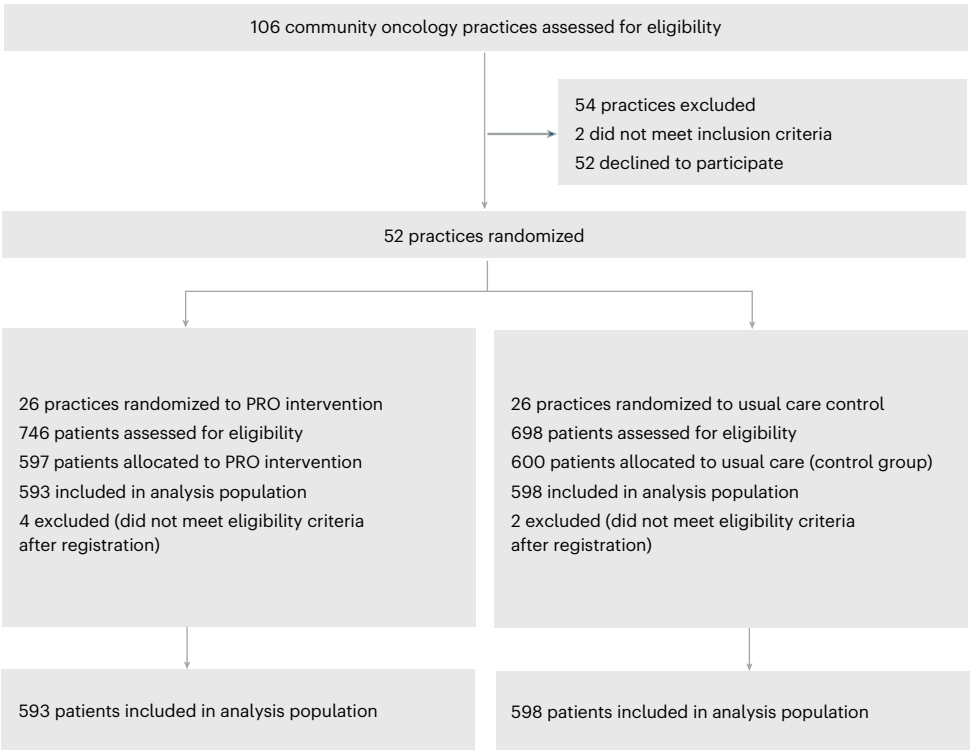

Fig. 1 | Recruitment, randomization and follow-up in the PRO-TECT trial.

group compared to usual care, with an HR of 0.84 (95% CI, 0.71–0.98, $P = 0.03$) (Fig. 3). The cumulative incidence of an emergency department visit at 12 months (that is, the proportion of patients visiting an emergency department) was 6.1% lower in the PRO group, specifically 48.7% (95% CI, 44.7%–53.0%) for PRO and 54.8% (95% CI, 50.9%–59.0%) for usual care. The mean number of emergency department visits per patient at 12 months was statistically significantly lower for PRO versus usual care (1.02 versus 1.30, $P < 0.001$). The proportion of patients with zero, one, two, three and four or more emergency department visits was 315/593 (53.1%), 136/593 (22.9%), 74/593 (12.5%), 30/593 (5.1%) and 38/593 (6.4%), respectively, in the PRO group and 273/598 (45.7%), 157/598 (26.3%), 73/598 (12.2%), 44/598 (7.4%) and 51/598 (8.5%), respectively, in the usual care group.

Time to deterioration of quality of life

Time to deterioration (that is, clinically meaningful worsening) in physical function, symptom control and HRQL secondary outcomes are shown in Fig. 4. Time to deterioration in physical function was statistically significantly longer in the PRO group compared to the control group, with a median time of 12.6 months versus 8.5 months (HR 0.73; $P = 0.002$). Findings were similar for symptom control (median 12.7 versus 9.9 months, HR 0.69; $P < 0.001$) and HRQL (median 15.6 vs 12.2 months, HR 0.72; $P = 0.001$).

When considering deaths in these analyses, differences between groups remained statistically significant. Specifically, time to death or deterioration was significantly longer in the PRO intervention group compared to usual care control for physical function (median 8.7 versus 6.3 months, HR 0.81; $P = 0.003$), symptom control (median 9.1 versus 7.5 months, HR 0.79; $P < 0.001$) and HRQL (median 10.3 versus 8.3 months, HR 0.81; $P = 0.004$).

Satisfaction

As previously described[16], 496 patient participants completed satisfaction feedback questionnaires at 3 months following enrollment, and 245 patient participants completed satisfaction feedback questionnaires at the off-study time point. Through this feedback, most patients noted that the weekly PRO symptom surveys were relevant to them (91.4% (350/383) at 3 months; 90.3% (214/237) at off-study), improved discussions with the care team (72.5% (359/495) at 3 months; 77.0% (188/244) at off-study), were used by the care team to make decisions (70.0% (345/493) at 3 months; 80.7% (196/243) at off-study), made them feel more in control of their care (77.1% (381/494) at 3-months; 84.0% (205/244) at off-study) and would recommend the system to other patients (89.3% (443/496) at 3-months; 91.4% (223/244) at off-study). Most patients felt the PRO system was easy to use (93.3% (463/496) at 3 months; 93.4% (227/243) at off-study) and the surveys were easy to understand (95.0% (471/496) at 3 months; 95.0% (230/242) at off-study).

Safety

No safety issues related to the process of digital symptom monitoring were reported.

Discussion

In a multicenter, randomized clinical trial comparing electronic PROs for symptom monitoring versus usual care during cancer treatment, there was no statistically significant difference in overall survival between groups. However, there were statistically significant reductions in emergency department visits and prolonged preservation of physical function, symptom control and HRQL among patients using PRO compared to usual care. In this population of patients living with advanced cancer and a high symptom burden, improvements in quality of life and physical functioning are critically important. These findings demonstrate that outcomes that are meaningful to patients are improved by this PRO intervention, which is nontoxic, inexpensive and considered valuable by patients[16]. These findings add to the results of prior studies showing substantial benefits of PRO symptom monitoring on clinical outcomes and utilization of emergency and hospital services[7,9–14], and cost savings[17,18], during cancer care.

The benefits observed in this trial may be due to a number of mechanisms. Identifying symptoms caused by cancer or treatments

https://doi.org/10.1038/s41591-025-03507-y

Table 1 | Patient characteristics at baseline

	PRO Intervention *n*=593	Usual Care Control *n*=598
Age, median (range), years	64 (29–89)	62 (28–93)
Sex		
Female	359/593 (60.5%)	335/597 (56.1%)
Male	234/593 (39.5%)	262/597 (43.9%)
Race (regardless of ethnicity)		
American Indian or Alaska Native	11/588 (1.9%)	13/576 (2.3%)
Asian	2/588 (0.3%)	16/576 (2.8%)
Black or African American	99/588 (16.8%)	94/576 (16.3%)
Native Hawaiian or Pacific Islander	2/588 (0.3%)	1/576 (0.2%)
White	473/588 (80.4%)	452/576 (78.5%)
Multiple races reported	1/588 (0.2%)	0/576 (0.0%)
Hispanic ethnicity (regardless of race)	14/591 (2.4%)	39/596 (6.5%)
Weekly PRO survey mode of administration (intervention group only)		
Internet	378 (63.7%)	N/A
Automated telephone	215 (36.3%)	N/A
Education		
First to eighth grade	10/592 (1.7%)	14/596 (2.3%)
Ninth to eleventh grade	35/592 (5.9%)	49/596 (8.2%)
High school graduate/GED	173/592 (29.2%)	187/596 (31.4%)
Some college, associate's degree, or other certification	218/592 (36.8%)	203/596 (34.1%)
College degree	91/592 (15.4%)	93/596 (15.6%)
Advanced degree	65/592 (11.0%)	50/596 (8.4%)
Employment status		
Full time (≥40 hours/week)	94/592 (15.9%)	89/596 (14.9%)
Part time	72/592 (12.2%)	48/596 (8.1%)
Not currently working	426/592 (72.0%)	459/596 (77.0%)
Rural practice location[a]	154/593 (26.0%)	163/598 (27.3%)
Marital status		
Married/partnered	385/593 (64.9%)	349/597 (58.5%)
Single, never married	58/593 (9.8%)	75/597 (12.6%)
Separated/divorced	82/593 (13.8%)	110/597 (18.4%)
Widowed	68/593 (11.5%)	63/597 (10.6%)
Technology use		
Never use a computer, tablet, or smartphone	62/593 (10.5%)	81/597 (13.6%)
Never use the internet	87/593 (14.7%)	114/597 (19.1%)
Never use email	114/593 (19.2%)	158/597 (26.5%)
Difficulty paying monthly bills		
Not at all	260/592 (43.9%)	224/596 (37.6%)
Not very	106/592 (17.9%)	127/596 (21.3%)
Somewhat	161/592 (27.2%)	184/596 (30.9%)
Very/extremely	65/592 (11.0%)	61/596 (10.2%)
Cancer type		
Colorectal, anal	100 (16.9%)	132 (22.1%)
Thoracic (lung, thyroid, thymus)	118 (19.9%)	110 (18.4%)
Breast	97 (16.4%)	80 (13.4%)
Gynecologic (ovarian, cervix, uterine, vaginal)	64 (10.8%)	53 (8.9%)
Pancreas, hepatobiliary	48 (8.1%)	49 (8.2%)
Gastroesophageal, small bowel	25 (4.2%)	38 (6.4%)
Genitourinary nonprostate (bladder, kidney, testicular, penile)	36 (6.1%)	26 (4.3%)
Myeloma, lymphoma	31 (5.2%)	31 (5.2%)
Prostate	33 (5.6%)	18 (3.0%)
Melanoma, skin	11 (1.9%)	21 (3.5%)
Other (brain, sarcoma, other soft tissue, head/neck, unknown primary)	30 (5.1%)	40 (6.7%)
Palliative care consult in past 12 months	51 (8.6%)	94 (15.7%)
Line of cancer therapy at study enrollment		
First line	206 (34.7%)	236 (39.5%)
Second line	176 (29.7%)	193 (32.3%)
Third line	102 (17.2%)	89 (14.9%)
≥Fourth line	109 (18.4%)	80 (13.4%)
Time since first diagnosis to metastatic cancer, median (interquartile range), months	0.7 (0.0–20.5)	0.7 (0.0–19.6)
Time since first diagnosis to initial treatment, median (interquartile range), months	1.2 (0.7–2.6)	1.3 (0.7–2.6)
Time since metastatic cancer diagnosis to study enrollment, median (interquartile range), months	10.4 (3.2–25.3)	11.4 (3.8–25.4)

GED, General Educational Development certificate; N/A, not applicable. [a]Rural/urban practice location based on US Census Bureau data (County Rurality Census Table), confirmed with practice self-designation.

early, before they worsen, may prevent downstream complications, such as erosion of physical function or quality of life, that would otherwise lead to emergency visits. The increased communication between providers and patients through the intervention may also optimize care coordination and patient engagement, which themselves may yield benefits. Educational materials provided to patients through the intervention may have fostered self-efficacy by patients.

Amidst this mounting evidence, there is increased interest in including PROs as an element of value-based cancer care delivery[19]. For example, the U.S. Centers for Medicare & Medicaid Services' initiated the Enhancing Oncology Model in 2023, which includes routine PRO collection, as do other international governmental payers[13]. PROs are also integrated in some commercial electronic health record (EHR) systems and included in international clinical practice guidelines[20,21]. The Patient-Centered Outcomes Research Institute funded the OncoPRO initiative in 2024, which provides US oncology practices with training materials, coaching and co-learning sessions to support implementation and sustainability of PRO symptom monitoring.

Nonetheless, PROs are still not widely implemented or reimbursed in cancer care[22]. Effective implementation requires practice-level efforts and costs, including education of patients, staff and providers; integration with nursing workflow and care coordination processes; modification of information systems; and ongoing program evaluation[21,23–26]. A previously published analysis of clinician feedback in this trial found that although nurses highly valued the PRO intervention for quality care delivery, documentation, communication and efficiency, they also expressed the need for dedicated time for PRO-related activities and integration with clinical processes and

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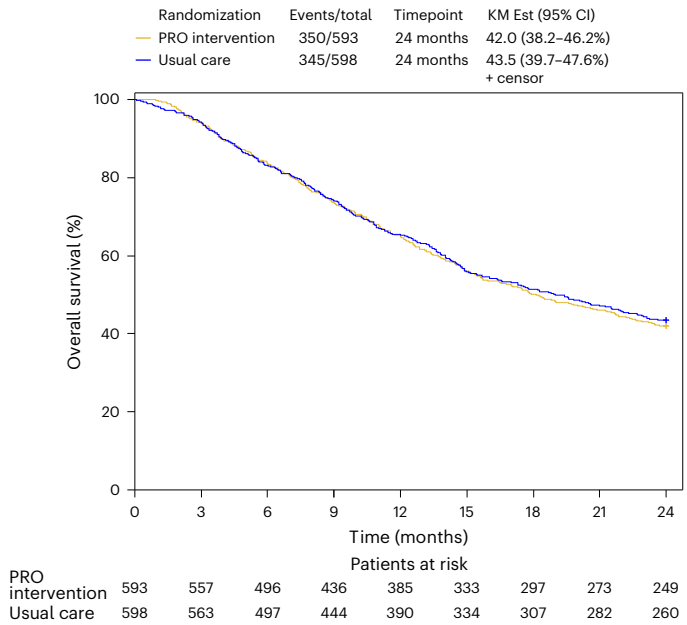

Fig. 2 | Overall survival in the PRO-TECT trial. All deaths were included in the analysis. Patients without observed deaths were censored on the last date known alive within the 2-year follow-up period based on medical chart abstraction and National Death Index administrative data. The unadjusted Kaplan-Meier estimated survival at 2 years (KM Est) was 42.0% (95% CI, 38.2%–46.2%) for the PRO intervention group and 43.5% (95% CI, 39.7%–47.6%) for usual care control. Overall survival was analyzed using Cox regression with prespecified covariates of line of systemic cancer treatment, months since first diagnosis to metastatic cancer, months since first diagnosis to initial treatment, months since metastatic cancer to study enrollment and a random effect to account for site clustering.

the EHR[16]. Therefore, reimbursement to support these necessary practice-level activities is essential to enable wider uptake. In the United States, there are now Current Procedural Terminology (CPT) billing codes for Remote Therapeutic Monitoring that may apply to the approach to PRO symptom monitoring used in this trial.

Completion rates of weekly surveys were high in this trial, on average 91.5%, demonstrating the feasibility of PRO symptom monitoring in clinical practice when using best practices for PRO implementation[20,21,25]. There are several likely reasons for these high completion rates. The PRO system was easy to use and simple for patients. Patients were given a choice of using either the web or an automated telephone system to answer surveys (with similar completion rates between these interfaces), which allowed patients to select an interface that was best suited to their preferences and abilities. For example, patients without a smartphone or broadband data access or with vision or tactile difficulties could choose the automated telephone system, whereas patients with mobile telephone range limitations or hearing difficulties could choose to use the web. Notably, patients in this trial who selected the automated telephone system over web were overall older, more rural and had less educational attainment, suggesting that more vulnerable patient populations can benefit from access to a telephone-based option. Providing an automated telephone interface option enables a more inclusive approach to this intervention. In addition, a backup data collection approach was used in which a staff member would call patients who did not respond to automated prompts, which may have increased patient engagement with the intervention.

A strength of this trial is inclusion of patients with varied backgrounds, including more than one-fifth who self-identified as Black, Indigenous, Hispanic, Asian and other people of color; about 40% with high school education or less; more than one-quarter treated at rural practice locations; and more than 15% who 'never' used the internet at baseline. Patients were drawn from 25 different US states, with a multitude of cancer types. The results demonstrate the feasibility and benefits of implementing PROs in real-world cancer populations.

Findings from this trial also demonstrate that use of the National Cancer Institute's PRO-CTCAE item library for remote symptom monitoring during routine clinical practice is both feasible and beneficial to patients. The PRO-CTCAE has previously been validated in a real-world routine care setting, and this trial now provides conclusive evidence supporting implementation of the PRO-CTCAE as a standard instrument for symptom monitoring in routine cancer care.

This trial has several limitations. Benefits may not have been experienced by all patients, and future research could aim to identify if certain subpopulations may particularly benefit. The outcome metrics may not reflect the full spectrum of value to patients, and other benefits on patient experience may warrant future evaluation, such as measures of engagement, communication, self-efficacy or content of visit discussions. Surveys were only available in English, Spanish and Mandarin, and additional languages could be offered in the future; there are now more than 70 languages available for the PRO-CTCAE.

Several prior studies have found improved survival associated with PRO symptom monitoring during cancer treatment[11–13]. These improvements have likely been attributable to the downstream impacts of early symptom detection and management, including better patient functioning, avoidance of hospitalizations, and lengthened duration of cancer treatment, all of which can confer mortality benefits[11]. In contrast, survival benefits with PROs were not observed in this trial. There are several potential reasons for this difference. First, this trial was partially conducted during the COVID-19 pandemic, when clinical and research staff and resources were strained and there were frequent disruptions in cancer care that may have negatively impacted disease outcomes overall (patients were enrolled in the trial through March 2020, and followed through March 2022). The magnitude of benefits

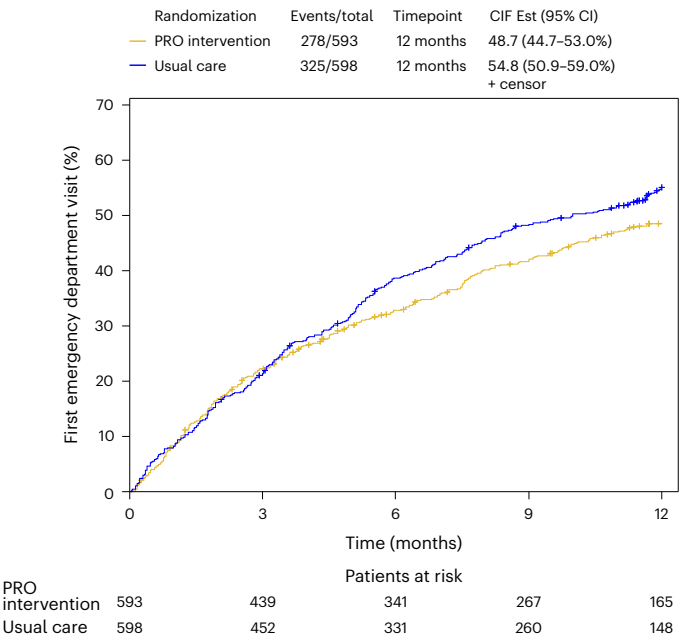

Fig. 3 | Cumulative incidence of first emergency department visit. The time to first emergency department visit was statistically significantly prolonged (improved) in the PRO intervention group compared to control, with an HR of 0.84 (95% CI, 0.71–0.98, two-sided $P = 0.03$). Time to first emergency department visit was analyzed using Fine-Gray competing risk regression with death as a competing event and with stratification by site to account for site clustering. Prespecified covariates of line of systemic cancer treatment, months since first diagnosis to metastatic cancer, months since first diagnosis to initial treatment, months since metastatic cancer to study enrollment and a random effect to account for site clustering were incorporated into the competing risk analysis.

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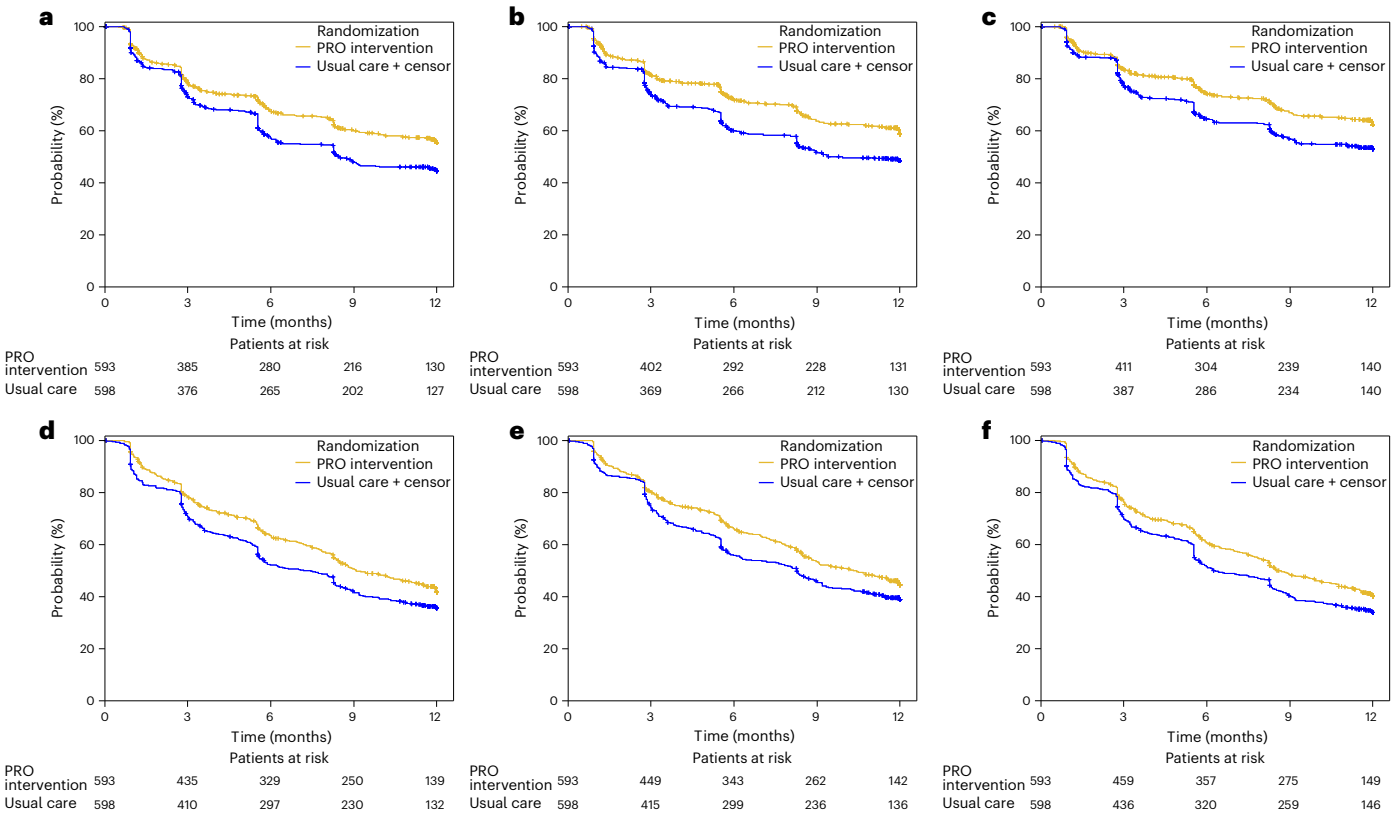

Fig. 4 | Time to deterioration of quality of life. a–**f**, Kaplan-Meier curves of time to deterioration (that is, clinically meaningful worsening) in (**a**) physical function, (**b**) symptom control, and (**c**) HRQL, and time to death or deterioration in (**d**) physical function, (**e**) symptom control and (**f**) HRQL, by randomization group. Time to deterioration in physical function was statistically significantly longer (improved) in the PRO group compared to the usual care control group, with a median time of 12.6 months versus 8.5 months (HR 0.73; $P = 0.002$). Findings were similar for symptom control (median 12.7 versus 9.9 months, HR 0.69; $P < 0.001$) and HRQL (median 15.6 versus 12.2 months, HR 0.72; $P = 0.001$). When considering deaths in analyses, time to death or deterioration remained statistically significantly longer (improved) in the PRO group compared to usual care control group for physical function (median 8.7 versus 6.3 months, HR 0.81; $P = 0.003$), symptom control (median 9.1 vs 7.5 months, HR 0.79; $P < 0.001$) and HRQL (median 10.3 versus 8.3 months, HR 0.81; $P = 0.004$). Analyses were conducted between groups using Cox regression including covariates of line of systemic cancer treatment, months since first diagnosis to metastatic cancer, months since first diagnosis to initial treatment, months since metastatic cancer to study enrollment and a random effect to account for site clustering. All P values are two-sided.

may therefore have been muted. Moreover, PRO symptom monitoring is intended to identify problems that patients are experiencing, and to communicate that information to care teams through alert notifications that may prompt actions. However, if care teams are diminished or preoccupied, as they were during the pandemic, they may not have the capacity to fully respond to alert notifications, thereby yielding a less effective intervention.

Second, the cluster randomized design of this trial appears to have introduced systematic baseline imbalances between randomization groups, possibly via practices assigned to the intervention selectively enrolling patients differently from practices assigned to usual care. Evidence of this is seen in baseline characteristics differences, with about 7% more patients receiving third-line or higher cancer therapy and 7% fewer receiving palliative care services in the PRO intervention group compared to usual care control. This difference indicates more advanced disease that may have been less well clinically addressed through supportive care among PRO intervention patients. This difference would have occurred if intervention practices selectively enrolled patients they felt might most benefit from PRO monitoring. Based on these observations, future trials of similar interventions are advised to avoid cluster randomized designs and rather utilize patient-level randomization.

Third, this trial was conducted in 52 large community practices across 25 different US states, with only small subsets of cancer patients at each practice participating in the trial. Therefore, deep integration with care processes and information systems like the EHR was not possible, which is increasingly recognized as a core component of successful PRO implementation[25–27]. A challenge when conducting research embedded within routine care delivery is that practice workflows, information flows and personnel roles are not changed as they might be with a true implementation. Therefore, the full impact of an intervention may not be realized, particularly when the intervention relies on personnel actions as with the PRO intervention in this trial.

Fourth, navigation services and patient portal systems are becoming more widely deployed in oncology practices, which may themselves improve communication between patients and providers[27], thereby blunting the observed isolated effects of PROs.

Nonetheless, the statistically significant and clinically meaningful positive benefits observed in this trial despite the above limitations provide evidence of the value of PRO monitoring in cancer care delivery. In the current era of emerging patient-centered oncology, future trials of symptom monitoring should emphasize outcomes that are proximate to the intervention and meaningful to patients beyond survival, including measures of how patients feel and function.

In conclusion, this national, multicenter, randomized clinical trial in adults with metastatic cancer demonstrates that symptom monitoring with PRO meaningfully improves clinical outcomes, the patient experience and utilization of services. The implication is that

a noninvasive, nontoxic and digital approach to engaging patients can enhance the impact of cancer treatment and complement other support services and should be included as a standard part of quality cancer clinical care.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-025-03507-y.

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https://doi.org/10.1038/s41591-025-03507-y

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Methods

Setting

PRO-TECT (Alliance AFT-39; NCT03249090) was a multicenter cluster randomized trial comparing electronic PRO symptom monitoring versus usual care. Oncology practices were the units of randomization, comprised of 52 community oncology practices in the national US network, the Alliance for Clinical Trials in Oncology (www.allianceforclinicaltrialsinoncology.org). Practice locations spanned 25 different US states, with 14 of the practices (26.9%) designated as rural based on US Census Bureau data (7 per randomization group). Characteristics of each practice were previously reported[15].

Patients and inclusion criteria

Each practice could enroll up to 50 consecutively approached adults (aged 21 years or older) with any type of metastatic cancer receiving outpatient systemic antineoplastic treatment (including immunotherapy, targeted oral therapy or chemotherapy), if they understood English, Spanish or Mandarin. Patients were excluded if they had indolent lymphoma or acute leukemia, were receiving hormonal monotherapy, had cognitive deficits that would preclude understanding of the consent form and/or study questionnaire or were participating in a therapeutic clinical trial. Potentially eligible patients were identified by practice-level research staff by reviewing ambulatory clinic and infusion schedules then discussing eligibility with treating clinicians. Eligible patients were then approached by the practice research staff and were invited to participate.

Ethics and consent

All patient participants signed written informed consent. The protocol and consent were approved by the Institutional Review Board (IRB) of the University of North Carolina (IRB Number 17-1864), as well as the Quorum central IRB (IRB number 32498) and the Advarra central IRB (IRB number Pro00043507). The sponsoring organization was the Alliance for Clinical Trials in Oncology (Protocol AFT-39). The protocol and statistical analysis plan were finalized prior to data analysis.

Patient Input

Patient input was included in every step of the design, conduct, and analysis of this trial. Virtual advisory meetings were held quarterly for presentation of progress and collection of feedback. Presentations to the Alliance Patient Advocate Committee twice annually also collected feedback. Three patient representatives served as investigators and are authors on this publication (PAS, JP, CG).

Randomization

Participating practices were randomly assigned 1:1 to electronic PRO symptom monitoring (intervention) or usual care (control) using permuted blocks with block sizes of 2 or 4 and stratified by rural/urban based on US Census Bureau criteria. A cluster-randomized design was selected with the intention to avoid potential spillover of enhanced attention to symptom management in control group patients. The unintended consequence of cluster randomization of an imbalance in baseline patient characteristics between groups was unforeseen, and therefore a cluster approach would not be considered advisable in future trials of symptom monitoring.

Intervention

Practices randomized to the intervention were provided with access to an electronic PRO monitoring system[28] which was developed based on prior research with high levels of usability[29,30]. This system administers surveys to patients with symptom questions from the National Cancer Institute's PRO-CTCAE[31,32] item library including constipation, diarrhea, dyspnea, insomnia, nausea, pain, and vomiting; as well as a depression item from the PHQ-2; an oral intake (eating and drinking) item; physical function from the patient-reported version of Eastern Cooperative Oncology Group performance status[33]; falls; and financial toxicity from the COST questionnaire[34] (Supplementary Table 1). At the end of each weekly PRO survey, patients could indicate if they were experiencing any additional symptoms with a 'free text' item[35]. Patients could choose to complete the surveys using either a web-based interface that automatically configures for use on either computers or handheld devices or an 'interactive voice response' automated telephone interface in which a recorded voice administers questions that are answered using pushbutton numerical responses.

Patients in the PRO intervention group received a brief (5 min) training by clinic staff on how to use the PRO monitoring system and then were instructed to complete surveys using the PRO monitoring system weekly for 1 year, or until voluntary disenrollment or discontinuation of all cancer treatment. A reminder prompt to complete the survey was sent to each patient on a day of the week and time they selected, via either an email or automated telephone call (patient's choice). A repeat reminder prompt was sent if the survey was not completed within 24 h, followed by a telephone call from a clinic staff member to administer the survey verbally if the survey was not completed electronically within 72 h.

Whenever a patient reported a prespecified level of magnitude or worsening of a PRO question compared to the prior survey (Supplementary Table 1), they received a link to patient education materials for self-management of that symptom. In addition, an automated email alert notification was forwarded to a clinical nurse responsible for that patient's care with the PRO score(s) and professional-level symptom management recommendations. At follow-up clinic visits, reports showing the longitudinal patterns of PROs were available through the system for nurses and oncologists to review. The PRO system was a freestanding electronic platform that was not integrated with the EHR systems of participating practices. Care team actions in response to alerts were at the discretion of clinicians.

Practices received online access to standardized educational pamphlets for managing symptoms, including clinician-level and patient-level materials. These materials were developed based on clinical practice guidelines and best available evidence. These materials were made available to patients by print at enrollment.

Control

Practices randomized to usual care control received online access to the same standardized clinician-level and patient-level educational pamphlets for managing symptoms as intervention practices. These materials were made available to patients by print at enrollment, the same as for patients enrolled at intervention practices. Patients enrolled at control-arm practices otherwise received usual care at the discretion of their local care teams and did not receive access to the PRO system.

Outcomes

The primary outcome of overall survival was defined as time from patient enrollment to death due to any cause. All participating patients were followed for 2 years from date of enrollment or until death, and all deaths were included in the analysis. Date of death was based on U.S. National Death Index administrative data[36] matched for patient name, sex, race, social security number (last four digits), date of birth and last known state of residence. These dates were confirmed with medical chart abstraction. In cases of discrepant dates of death, standardized reconciliation included site queries, confirmation of patient demographics, obituary searches and outreach to next of kin[37].

Prespecified secondary outcomes included the quality of life scales of physical functioning, symptom control and HRQL. Results for these scales were previously reported but did not include analyses of time to deterioration and could not incorporate survival data, because dates of death were not yet available. An updated analysis was prespecified to occur with availability of survival data to compare time to death or deterioration of quality of life scales between groups. The source of data for the quality of life scales was patient completion of the

European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire[38], on paper or electronically, at enrollment and 1, 3, 6, 9 and 12 months following enrollment. The QLQ-C30 is a 30-item questionnaire and has been shown to have robust measurement properties[39]. Standardized assessment of physical function is based on 5 items that generate a single score, symptom control is based on a composite of 8 symptom scale scores[40] and HRQL is assessed by combining function and symptom scale scores[41]. An additional prespecified outcome was emergency department visits within one year after enrollment based on medical chart abstraction.

As previously described, the secondary outcome of patient satisfaction was ascertained via a feedback questionnaire[16,25] administered to each enrolled participant at 3 months following enrollment and at the time of going off-study if the patient was able. Duration of cancer therapy was initially included as a secondary outcome but was removed as an outcome in the Statistical Analysis Plan prior to data analyses due to infeasibility of collecting this information across participating practices, and financial outcomes were previously reported[42].

Race and ethnicity information were collected directly from patients and categorized based on fixed categories.

Safety

The trial was monitored by the study team and IRB. No data safety and monitoring board was included for this trial, as there were not considered to be safety concerns associated with survey administration. Instructions were included for patients during training and in surveys to contact their care team directly for medical concerns and not to rely on surveys as the sole means for communicating symptoms or other concerns to the care team. Participating practices were instructed to report any safety concerns to the study team.

Remuneration

Patient participants in both groups received up to $150 total as remuneration for their effort and time completing a research demographics form and the QLQ-C30 quality of life outcomes questionnaire. This amount was divided evenly into $75 at enrollment and $75 at 3 months.

Sample size calculation

The initial study protocol, approved 27 July 2017, included 1,000 patients from 50 sites and was amended on 17 January 2019 to increase the sample size to 1,200 patients from 52 sites. This sample size provided 90% power for an overall survival hazard ratio of 0.76 based on prior research[15] using a two-sided alpha of 0.05 log-rank test with 576 observed events, computed using the formula by Xie and Waksman[43], with an intracluster correlation coefficient of 0.001 (based on prior trials), assuming dropout of 150 patients in the first 2.5 years.

Enrollment to the trial was discontinued on 23 March 2020 with 1,191/1,200 (99.3%) planned enrollees because of the COVID-19 pandemic's impact on the ability of practice research staff to approach and enroll patients.

Statistical analysis

The outcome of overall survival was analyzed via Cox regression using prespecified covariates of months since initial diagnosis to development of metastases, months since initial diagnosis to first systemic cancer treatment, line of sustemic cancer treatment, months since developing metastases to date of trial enrollment and a random effect for site clustering. All deaths were included in the analysis. Patients without observed deaths were censored on the last date known alive within the 2-year follow-up period based on medical chart abstraction and National Death Index administrative data[36]. Heterogeneity of effect was explored by a series of Cox regression models in which individual categorical covariates were included in the primary Cox regression model along with a covariate-by-randomization group interaction effect. Results were explored in a forest plot.

Impact of randomization group on time to first emergency department visit was analyzed using Fine-Gray competing risk regression with death as a competing event and with stratification by site to account for site clustering. The same covariates as the overall survival analysis were incorporated into the competing risk analysis. Number of emergency department visits was also explored using a marginal means/rates model. The number of emergency department visits per patient was tabulated for each group as zero, one, two, three and four or more. Mean number of emergency department visits was compared between arms using a mixed model. Each model included all available data from all patients according to their randomization group. Fixed effects included randomization group and cancer diagnosis related covariates (line of systemic cancer treatment, months since first diagnosis to metastatic cancer, months since first diagnosis to treatment and months since metastatic cancer to study enrollment). A random practice intercept term was included to account for clustering by practice.

Analyses of time to deterioration in quality of life scales (that is, time to worsening by a clinically meaningful score change), and time to deterioration in quality of life scales or death, were conducted between groups using Cox regression. The prespecified quality of life scales were physical function, symptom control and HRQL from the EORTC QLQ-C30 (ref. 38). Time to deterioration was specifically defined as the first 10-point decline from baseline, which is established as a clinically meaningful change for QLQ-C30 scales[44]. Time to death or deterioration was specifically defined as time to deterioration in quality of life scales, or death from any cause, within 12 months. Each Cox regression model included covariates of line of systemic cancer treatment, months since first diagnosis to metastatic cancer, months since first diagnosis to initial treatment, months since metastatic cancer to study enrollment and a random effect to account for site clustering. Patients without observed quality of life decline, or death for the combined analysis, were censored at the last date that a quality of life questionnaire was completed.

Descriptive statistics were employed for the analyses of satisfaction questionnaires, and completion of weekly symptom surveys was tabulated for each patient as the number of completed surveys divided by the number of surveys that were expected to be completed.

The study database was frozen on 4 October 2022. Statistical testing was two sided, with P values < 0.05 considered statistically significant, and carried out in SAS v9.4 (SAS Institute).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Individual deidentified participant data for this trial, including data dictionaries and all variables from analyses in this publication, are available through the Alliance for Clinical Trials in Oncology. Data Sharing Requests may be submitted at: https://www.allianceforclinicaltrialsinoncology.org/main/public/standard.xhtml?path=%2FPublic%2FDatasharing. Any investigator may submit a data request, which includes the investigator's name, institution and contact information; the requested data elements; and the purpose of the data request. Once received, the request is forwarded to the Alliance Statistics and Data Management Center (SDMC), which confirms availability of the data and then sends a Data Release to the investigator. Once the data release is received from the requesting investigator, the requested data may be released. Questions about this process may be directed to DataSharing@AllianceNCTN.org.

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Acknowledgements

We thank N. Arora for his guidance and support during the conduct of this research. In addition, we extend our gratitude to the patients who participated in this trial and their caregivers, as well as to the clinical and research personnel at participating practices who made this work possible, often despite the challenges of the pandemic. This trial was funded by the Patient-Centered Outcomes Research Institute (PCORI) IHS-1511-33392, with research support from this grant provided to all authors listed on this manuscript except V.B. and A.W. The trial made use of technology systems provided by the Patient-Reported Outcomes Core (PRO Core) at the Lineberger Comprehensive Cancer Center of the University of North Carolina, which is funded by National Cancer Institute Cancer Center Core Support Grant 5-P30-CA016086 and the University Cancer Research Fund of North Carolina. None of the funders of this trial have any rights to reviewing, editing, or withholding any aspect of the research or publications. The trial was sponsored by the Foundation of the Alliance for Clinical Trials in Oncology (https://acknowledgments.alliancefound.org), which reviewed and approved this publication but has no rights to alter the content or withhold publication except for errors of fact or accuracy.

Author contributions

E.B., D.S. and A.C.D. participated in the design, conduct and analysis of the trial and reviewed/signed off on the final version of the manuscript. J.J., S.H., P.C., M.J. and L.R. participated in the data management for the trial and reviewed/signed off on the final version of the manuscript. B. Ginos and A.M.D. participated in statistical analysis for the trial and reviewed/signed off on the final version of the manuscript. A.M.S., P.A.S., A.V.B., G.T., B.B.R., C.S., D.B., D.C., L.A.K., J.P., C.G., B. Given, G.L.M., R.M., J.F.S., D.M.Z., A.W., V.S.B. and A.P.W. participated in the design of the trial, provided input in the interpretation of findings and reviewed/signed off on the final version of the manuscript.

Competing interests

E.B. received personal fees from Navigating Cancer, AstraZeneca, Resilience, Thyme Care, N-Power Medicine, Verily and the Research Triangle Institute as a scientific advisor. D.S. received personal fees from Pfizer. A.M.S. received personal fees from UroGen Pharma and research funds to her institution from Pfizer Global. P.A.S. received personal fees from Pfizer. G.T. received research funds to her institution from Seagen and Novartis. C.S. received personal fees from Shionogi and Movember and research funds to her institution from Pfizer and Genentech. R.M. is employed by ConcertAI and received meal reimbursements from AstraZeneca. D.C. is the president of FACIT.org and an uncompensated board member of the PROMIS Health Organization. L.A.K. received research funds to her institution from Immunocore. A.W. received personal fees from Merck. The other authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-025-03507-y.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-025-03507-y.

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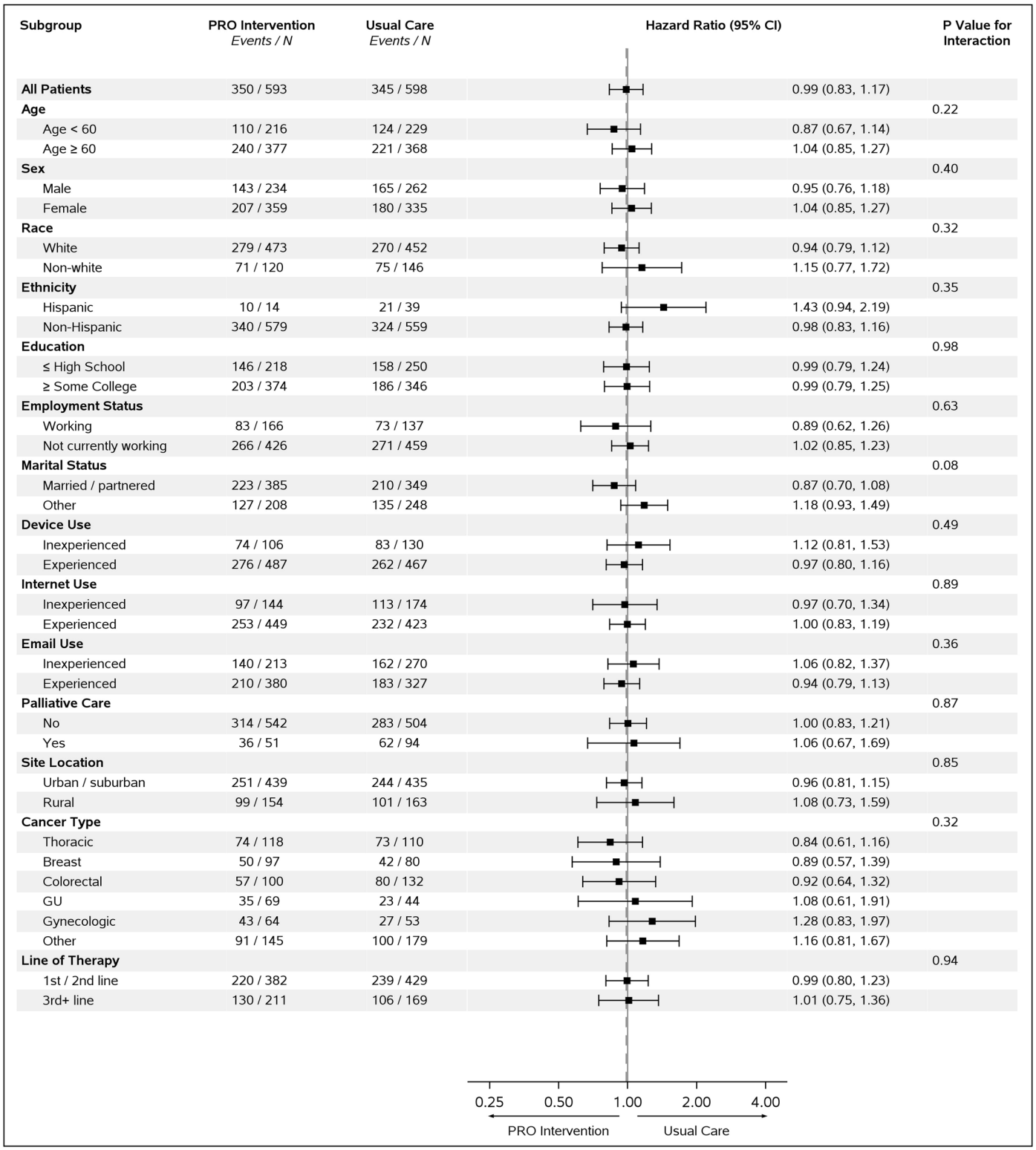
Peer review information *Nature Medicine* thanks Menggang Yu, Annie Young and Alicia Hong for their contribution to the peer review of this work. Primary Handling Editor: Ming Yang, in collaboration with the *Nature Medicine* team.

https://doi.org/10.1038/s41591-025-03507-y



Extended Data Fig. 1 | Forest plot of overall survival subgroup analyses. Within subgroups of patients defined by baseline covariates, no meaningful difference in overall survival was observed between randomization groups. The measure of centre represents an HR of 1.0, and the error bars represent the 95% confidence intervals.

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Last updated by author(s): Dec 20, 2024

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Research data and patient questionnaires were collected in an encrypted Oracle research database developed by PRO Core and hosted at University of North Carolina. Data transmitted between the server and end-users were also encrypted using SSL. More information about PRO Core services and systems is available at https://pro.unc.edu/about.
Data analysis	Statistical analysis was carried out using no custom algorithms within SAS v9.4.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

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Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex was obtained from patients using fixed categories. Patients were eligible regardless of sex and the study design did not depend on sex. Sex is reported in the baseline table (Table 1) and heterogeneity of effect on the primary outcome (overall survival) is reported in eFigure 1.
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity were obtained from patients using fixed categories. Patients were eligible regardless of race and ethnicity although patients were required to understand English, Spanish, or Mandarin Chinese to enroll, and the study design did not depend on race or ethnicity. Race and ethnicity is reported in the baseline table (Table 1) and heterogeneity of effect on the primary outcome (overall survival) is reported in eFigure 1.
Population characteristics	See above.
Recruitment	This was a cluster randomized trial. Practices were recruited for participation through standardized recruitment communications sent to practices within the Alliance Foundation network. Each practice could enroll patients meeting eligibility criteria. The enrollment approach may have been biased towards practices and patients interested in electronic patient-reported outcome interventions which may limit the generalizability of results to a broader population, and there is some indication that practices that were randomized to the control condition enrolled patients with less advanced disease relative to the intervention practices which may have biased results towards the control group.
Ethics oversight	This study was approved by a central IRB designated by the funder and by individual IRBs at each of the 52 participating sites.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences ☒ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	This is a cluster randomized controlled clinical trial that collected quantitative data including longitudinal patient surveys, clinical data, and patient outcomes. This trial also collected qualitative data from patients and site staff which has been reported in other publications. A cluster-randomized design was selected to avoid potential spillover of enhanced attention to symptom management in control group patients.
Research sample	52 practices meeting eligibility criteria were recruited and randomized from the Alliance Foundation network. Each practice could enroll up to 50 consecutively approached eligible patients. The sample is representative of US community oncology practices.
Sampling strategy	Participating practices were randomly assigned 1:1 to electronic patient-reported outcome symptom monitoring (intervention) or usual care (control) using permuted blocks with block sizes of 2 or 4 and stratified by rural/urban based on US Census Bureau criteria.
Data collection	Patients completed questionnaires either on paper or electronically via the web; patient questionnaire data were stored in a central research database. Electronic case report forms were housed in the same central research database and were completed by data coordinators at each site based on source data in the Electronic Health Record for clinical data such as emergency room visits. Date of death was extracted from the US National Death Index matched for patient name, sex, race, social security number (last four digits), date of birth, and last known state of residence. Dates were reconciled with data from the electronic case report forms.
Timing	First patient was enrolled on 10/31/2017, last patient was enrolled on 3/23/2020, and data were frozen for statistical analysis on 10/4/2022.
Data exclusions	54 practices were excluded during screening for not meeting inclusion criteria (n=2) or declining to participate (n=52); and 253 patients were excluded from practices for not meeting eligibility criteria after registration (n=6) or declining to participate (n=247). Data for all above practices and patients were excluded from analysis as planned.
Non-participation	54 practices were excluded during screening for not meeting inclusion criteria (n=2) or declining to participate (n=52); and 253 patients were excluded from practices for not meeting eligibility criteria after registration (n=6) or declining to participate (n=247).
Randomization	Participating practices were randomly assigned 1:1 to electronic patient-reported outcome symptom monitoring (intervention) or usual care (control) using permuted blocks with block sizes of 2 or 4 and stratified by rural/urban based on US Census Bureau criteria. Primary statistical analysis (comparison of overall survival) adjusted for prespecified covariates of line of systemic cancer treatment,

months since first diagnosis to metastatic cancer, months since first diagnosis to initial treatment, and months since metastatic cancer to study enrollment, and a random effect to account for site clustering.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	ClinicalTrials.gov NCT03249090
Study protocol	Submitted to ClinicalTrials.gov and pending public posting. Also published with Basch E, et al. JAMA. 2022 Jun 28;327(24):2413-2422.
Data collection	52 US community oncology practices participated by enrolling patients. Patient surveys and electronic case report forms were collected in a central research database housed at the University of North Carolina. The first patient was enrolled on 10/31/2017, the last patient was enrolled on 3/23/2020, and data were frozen for statistical analysis on 10/4/2022.
Outcomes	The primary outcome was overall survival. Patients were followed for 2 years after registration and vital status was reported in electronic case report forms by local practice data coordinators. Date of death was also extracted from the US National Death Index matched for patient name, sex, race, social security number (last four digits), date of birth, and last known state of residence. Death dates from the US National Death Index were reconciled with death dates from the electronic case report forms. Secondary outcomes included emergency room/hospital utilization at 1 year reported in electronic case report forms by local practice data coordinators. Secondary outcomes reported in prior publications include patient-reported Physical Function, Symptom Control, and Health-related Quality of Life at 3 months measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30; Basch E, et al. JAMA. 2022 Jun 28;327(24):2413-2422) and Patient Satisfaction/Communication at 3 months as measured by feedback surveys (Basch E, et al. JCO Clin Cancer Inform. 2020 Oct;4:947-957).