Title

Effects of the WRITE Symptoms Interventions on Symptoms and Quality of Life Among Patients With Recurrent Ovarian Cancers: An NRG Oncology/GOG Study (GOG-0259)

Journal

Journal of Clinical Oncology, 40(13)

ISSN

0732-183X

Authors

Donovan, Heidi S
Sereika, Susan M
Wenzel, Lari B
et al.

Publication Date

2022-05-01

DOI

10.1200/jco.21.00656

Peer reviewed

original reports

Effects of the WRITE Symptoms Interventions on Symptoms and Quality of Life Among Patients With Recurrent Ovarian Cancers: An NRG Oncology/GOG Study (GOG-0259)

Heidi S. Donovan, PhD, RN[1,2] ; Susan M. Sereika, PhD[1]; Lari B. Wenzel, PhD[3]; Robert P. Edwards, MD[2]; Judith E. Knapp, PhD[1]; Susan H. Hughes, RN, MSN[4]; Mary C. Roberge, RN, BSN[1]; Teresa H. Thomas, PhD, BA, RN[1]; Sara Jo Klein, MS, BSN[1]; Michael B. Spring, PhD[5]; Susan Nolte, PhD, RN[6]; Lisa M. Landrum, MD, PhD[7]; A. Catherine Casey, MD[8]; David G. Mutch, MD[9]; Robert L. DeBernardo, MD[10]; Carolyn Y. Muller, MD[11]; Stephanie A. Sullivan, MD[12]; and Sandra E. Ward, PhD, RN[4]

abstract

PURPOSE GOG-259 was a 3-arm randomized controlled trial of two web-based symptom management interventions for patients with recurrent ovarian cancer. Primary aims were to compare the efficacy of the nurse-guided (Nurse-WRITE) and self-directed (SD-WRITE) interventions to Enhanced Usual Care (EUC) in improving symptoms (burden and controllability) and quality of life (QOL).

METHODS Patients with recurrent or persistent ovarian, fallopian, or primary peritoneal cancer with 3+ symptoms were eligible for the study. Participants completed baseline (BL) surveys (symptom burden and controllability and QOL) before random assignment. WRITE interventions lasted 8 weeks to develop symptom management plans for three target symptoms. All women received EUC: monthly online symptom assessment with provider reports; online resources; and every 2-week e-mails. Outcomes were evaluated at 8 and 12 weeks after BL. Repeated-measures modeling with linear contrasts evaluated group by time effects on symptom burden, controllability, and QOL, controlling for key covariates.

RESULTS Participants (N = 497) reported mean age of 59.3 ± 9.2 years. At BL, 84% were receiving chemotherapy and reported a mean of 14.2 ± 4.9 concurrent symptoms, most commonly fatigue, constipation, and peripheral neuropathy. Symptom burden and QOL improved significantly over time ($P < .001$) for all three groups. A group by time interaction ($P < .001$) for symptom controllability was noted whereby both WRITE intervention groups had similar improvements from BL to 8 and 12 weeks, whereas EUC did not improve over time.

CONCLUSION Both WRITE Intervention groups showed significantly greater improvements in symptom controllability from BL to 8 and BL to 12 weeks compared with EUC. There were no significant differences between Nurse-WRITE and SD-WRITE. SD-WRITE has potential as a scalable intervention for a future implementation study.

J Clin Oncol 40:1464-1473.

INTRODUCTION

Approximately 21,400 individuals will be diagnosed with ovarian cancer in 2021.[1] Despite aggressive therapy, most experience a recurrence within three years.[2] After initial recurrence, goals shift to disease remission or stabilization and optimal symptom and quality of life (QOL) management.[3,4] Individuals typically receive a median of four additional lines of therapy after their first recurrence.[5] Aggressive treatment can lead to multiple severe symptoms and significant QOL impairments.[3,6] A 2016 National Academies report[7] called for novel self-management interventions to optimize quality and quantity of life. However, the process of symptom self-management can be overwhelming and time-consuming for both patients and clinicians. Interactive eHealth interventions are feasible and acceptable to a wide variety of clinical populations, ages, and ethnicities.[8-10] Health care systems, providers, and patients are turning to eHealth technologies to supplement face-to-face clinician support and reduce clinic time pressures. A web-based trial of symptom monitoring with automated symptom severity alerts to clinicians improved symptoms, QOL, and survival compared with usual care.[11,12] A systematic review of web-based interventions for cancer-related symptom management identified elements such as symptom monitoring, facilitated communication with providers, information, and automated symptom management support and feedback as most likely to improve symptoms.[13]

ASSOCIATED CONTENT

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on January 5, 2022 and published at ascopubs.org/journal/jco on February 7, 2022: DOI https://doi.org/10.1200/JCO.21.00656

CONTEXT

Key Objective

Individuals with recurrent ovarian cancer and their providers are challenged to manage multiple co-occurring cancer and treatment-related symptoms. This multisite randomized controlled trial (N = 497) evaluated whether an 8-week web-based symptom self-management intervention (WRITE Symptoms), either facilitated by a nurse or fully computer-mediated, could improve symptom burden, symptom controllability, and quality of life compared with enhanced usual care.

Knowledge Generated

Both WRITE Symptoms interventions significantly improved symptom controllability at 8 and 12 weeks compared with enhanced usual care. Although all three groups experienced reduced symptom burden and quality of life over time, there were no significant differences between groups.

Relevance

The web-based WRITE Symptoms intervention, regardless of delivery method, enhanced women's sense of control over their three target symptoms. The computer-mediated SD-WRITE is an efficient and scalable intervention with potential for implementation in clinical settings.

The WRITE Symptoms interventions built on the results of previous multisymptom management trials[14] and are based on the Representational Approach (RA) to patient education[15-17] derived from the Common-Sense Model of Illness Representations[18,19] and educational theory. The Common-Sense Model explicitly links representations to self-management behavior and the educational theory guides activities to promote both conceptual and behavioral change.[20-22] The RA emphasizes a detailed discussion of patients' symptom representations (beliefs) to guide relevant and specific symptom management recommendations. The RA and Nurse-guided WRITE Symptoms (Nurse-WRITE) have been described elsewhere[16,23] and are summarized in Table 1.

Nurse-WRITE is delivered by nurses via private internet message boards where patients interact with a nurse from the comfort of home. It provides a place for both patients and nurses to document discussions for review and reflection, and was designed to leverage the mood and problem-solving benefits of expressive writing.[42] A pilot study (NIH R21-NR009275) demonstrated that Nurse-WRITE was acceptable and feasible, and significantly reduced symptom distress and severity, compared with wait-listed control.[23] The web-based infrastructure for WRITE Symptoms delivery and a library of evidence-based Symptom Care Guides with medical and self-care strategies for 28 common symptoms were created for this trial. Recognizing that Nurse-WRITE is a complex and time-consuming process, we aimed to evaluate whether a self-directed web-based module could be a successful alternative. A computer-mediated (self-directed) version of WRITE Symptoms (SD-WRITE), following an identical process to Nurse-WRITE, was developed and validated by patients, theoretical, and clinical experts.[24]

This study compared the efficacy of *Nurse-WRITE* and *SD-WRITE* to Enhanced Usual Care (EUC) in improving target symptom burden and controllability (primary outcomes) and QOL (secondary outcome). We hypothesized that (1) at 8 or 12 weeks after baseline (BL), Nurse-WRITE would be superior to EUC, and (2) at 8 or 12 weeks post-BL, SD-WRITE would be superior to EUC. If (1) and (2) were true, exploratory analyses would compare Nurse-WRITE and SD-WRITE.

METHODS

Design

Participants were randomly assigned with equal allocation (1:1:1) to Nurse-WRITE, SD-WRITE, and EUC. Random assignments were generated using minimization, with race and ethnicity (non-Hispanic White *v* minority) as the stratification factor. Measures were obtained at BL and every 4 weeks for one year. The primary end points of the study were symptom burden, symptom controllability, and QOL at 8 and 12 weeks after BL.

Sample

Eligible participants were age 18+ years; with recurrent or persistent ovarian, fallopian tube, or primary peritoneal cancer; Gynecologic Oncology Group (GOG) performance status of ≤ 2; reporting at least three symptoms associated with cancer or treatment; able to read and write in English; and BL questionnaire completion within 28 days of study consent. Interested participants without access were provided tablet computers with cellular internet access.

On the basis of observed effect sizes from the Nurse-WRITE pilot study,[23] a group sample size of 96 was needed for 0.80 power with a standardized mean difference of d = 0.50 in symptom burden and controllability at 8 and 12 weeks relative to BL between Nurse-WRITE and EUC with two-sided hypothesis testing at $P < .025$ to adjust for multiple testing. Assuming at least a medium effect size of

TABLE 1. Study Activities for Participants in Each of the Three Treatment Conditions: EUC, SD-WRITE, Nurse-WRITE

Study Activities	EUC	SD-WRITE	Nurse-WRITE
Safety monitoring			
Q4 week symptom severity report sent to clinic	X	X	X
Phone call to Pp for distressing symptoms	X	X	X
Q2 week friendly e-mails	X	X	X
Resource library			
Links to quality online cancer and ovarian cancer resources	X	X	X
Links to symptom management resources		X	X
Evidence-based Symptom Care Guides for 28 symptoms (electronic and paper)		X	X

Elements of Representational Approach	EUC	SD-WRITE	Nurse-WRITE
Representational assessment			
Q4 week SRQ	X	X	X
Pp responds in writing to automated symptom representation assessment prompts		X	
Pp responds in writing to nurse assessment prompts followed by written discussion			X
Create conditions for conceptual change			
Provide information to address concerns from SMBQ		X	X
Discuss concerns and gaps in understanding and individualize to personal consequences			X
Provide new information			
Introduce Symptom Care Guide that includes evidence-based strategies for patient-clinician communication, adherence to clinician recommendations, and self-care		X	X
Direct to personally relevant parts of guide			X
Goal setting and strategy selection			
Prompt for Pp's goal		X	X
Assist with individualization of goal			X
Pp selects strategies from drop-down menu		X	
Discuss and individualize strategies			X
Develop symptom care plan			
Automated from goal and strategy prompt		X	
Individualized on the basis of RN and Pp discussion			X
Goal and strategy review and revision after 2 weeks			
Review of strategy use and effectiveness		X	X
Prompt to keep or change goal and strategies from drop-down menu		X	
RN assistance to refine goals and strategies			X

Abbreviations: EUC, enhanced usual care; ND, nurse-delivered; Pp, participant; RN, registered nurse; SD, self-directed; SMBQ, Symptom Management Barriers Questionnaire; SRQ, Symptom Management Questionnaire.

d = 0.405 for SD-WRITE, 144 participants per group were needed for sufficient power (≥ 0.80) to test for differences in the primary outcomes between SD-WRITE and EUC (hypothesis 2) with two-sided hypothesis testing at a significance level of $P = .025$. Accounting for attrition rates of 10% seen in the pilot study,[23] a target sample size of 480 (160 per group) was determined.

Recruitment

Potential participants were approached by certified research assistants (CRAs) at each participating GOG/NRG Oncology-affiliated site. CRAs evaluated eligibility (from medical record and symptom inventory assessment) and obtained informed consent if appropriate. A centralized consent form and institutional review board (IRB) proposal template was created; IRB approval was obtained at the University of Pittsburgh and each participating clinical site.

Data Collection Procedures

All study activities and questionnaires were conducted using the password-protected WRITE Symptoms website developed at the University of Pittsburgh, with features to

ensure accurate, secure, Health Insurance Portability and Accountability Act–compliant data collection. The public, application, and data systems were housed on separate secure servers.

Measures

Primary outcomes. Composite Symptom Burden and Symptom Controllability were assessed using the Symptom Representation Questionnaire (SRQ), a reliable and valid measure of symptom representations in individuals with ovarian cancer.[6] Participants complete a 28-item symptom inventory, reporting symptom severity (at its worst) in the past week from 0 (did not experience the symptom) to 10 (as bad as I can imagine). Participants then identify three target symptoms they would like to get better control over. Three additional subscales assess consequences (eg, impact on life and family; five items), distress (three items), and controllability (five items) for each target symptom on a 0 (strongly disagree) to 4 (strongly agree) scale. Target symptom burden[6] is a composite of the SRQ severity, consequences, and distress scales (transformed to a 0-10 scale). Target symptom controllability represents one's confidence in ability to control symptoms with medications or behaviors. In this study, Cronbach's $\alpha = .79$ for target symptom controllability and .90 for target symptom burden.

Secondary outcome. The Functional Assessment of Cancer Therapy—General, version 4 (FACT-G), assesses global QOL.[25] This scale is validated in ovarian cancer[26,27] and includes four well-being subscales: physical (seven items); social (seven items); emotional (six items); and functional (seven items). These subscales are aggregated to produce the total QOL score. Cronbach's $\alpha = .92$ in this study.

Potential time-invariant covariates (assessed at BL). The Revised Life Orientation Test (LOT-R) measured optimism.[28] This an eight-item scale with four filler questions. Response options range from 0 (agree a lot) to 4 (disagree a lot). Summed scores (range, 0-32) are used in analyses. LOT-R has strong reliability and validity as a trait measure, with established population norms and association with information seeking and goal setting.[29] Cronbach's $\alpha = .78$ in this study.

The well-validated 20-item trait anxiety subscale of the Spielberger State-Trait Anxiety Inventory (STAI) has been associated with increased sensitivity to symptoms.[30,31] Items assess how one generally feels on a 4-point scale from 1 (almost never) to 4 (almost always) and are summed for a total score. Cronbach's $\alpha = .90$ in this study.

The validated Interpersonal Support Evaluation List (ISEL) 12-item short-form assessed social support.[32-34] Response options range from 1 (definitely false) to 4 (definitely true); items are summed for a total score. Cronbach's $\alpha = .87$ in this study.

Sociodemographic characteristics were assessed with the Center for Research in Chronic Disorders Sociodemographic survey for age, race, ethnicity, education, and income.

Potential time-dependent covariates. The Symptom Management Barriers Questionnaire-Short Form (SMBQ-SF) was used to assess barriers to actively engaging in symptom management.[35-37] The SMBQ-SF addresses 16 attitudinal barriers to reporting and managing multiple symptoms. A count of endorsed items is used in analyses. Cronbach's $\alpha = .68$ in this study.

The well-validated Brief Center for Epidemiologic Studies-Depression (CES-D-10) scale measured the severity of depressive symptoms that interfere with problem-solving.[38,39] Items were rated on a 4-point Likert-type scale (0 = rarely or none of the time; 3 = all of the time) and summed to yield an overall score. Cronbach's $\alpha = .84$ in this study.

GOG forms were completed quarterly by GOG CRAs to document receipt of chemotherapy and hospitalizations during the previous assessment period.

Intervention Procedures

Participants completed BL measures and were randomly assigned to treatment condition through GOG's web-based randomization system using race and ethnicity as a pre-randomization stratification factor. Table 1 summarizes similarities and differences in study activities among treatment groups.

Safeguard Procedures

Symptom monitoring and reporting safeguards were implemented for participants in all groups. Automated reports of monthly SRQ symptom severity (0-10) ratings were monitored daily by research staff and sent to GOG sites. This was the only formal communication between research staff and GOG sites regarding patient symptoms.

Symptom distress ratings of 4 (on a 0-4 scale) triggered an automated e-mail to Pitt research staff who encourage participant to contact her health care provider. Webpages and print materials included prominent statements about the importance of communicating with health care providers about new or worsening symptoms.

EUC participants received symptom monitoring and reporting activities described above. In addition, participants had access to curated information on ovarian cancer and treatment on their WRITE Symptoms webpage.

SD-WRITE participants were assigned to an interactive computer module for 6-8 weeks. The module guided each participant through all elements of the WRITE Symptoms intervention to develop tailored Symptom Care Plans, followed by a 2-week strategy review and revision for each of participants' three target symptoms. Table 1 presents the key elements of SD-WRITE.

Nurse-WRITE participants were assigned to a password-protected private message board. One of four research nurse interventionists led the participant (1:1) through WRITE Symptoms via asynchronous postings on this message board. The nurse's goal was to develop

individualized Symptom Care Plans followed by a 2-week strategy review and revision for each participant's three target symptoms over 8 weeks adhering to a standardized protocol (Table 1). To ensure fidelity to the intervention, weekly nurse interventionist meetings were held to review intervention postings and to discuss fidelity reviews performed by H.S.D. and J.E.K.

Data Analysis

An exploratory data analysis was first performed to (1) describe data distributions; (2) identify associations between variables, including comparability of randomly assigned treatment groups, and need for covariate adjustment; (3) check for violations of assumptions underlying statistical techniques; (4) assess amount and patterns of missing data; and (5) evaluate psychometric properties of multi-item scales.

In keeping with intention-to-treat approach, all randomly assigned participants were retained in efficacy analyses. Repeated-measures modeling (covariance pattern modeling using linear mixed modeling methods) investigated the relationship of randomized group assignment with symptom burden, controllability, and QOL over time (at 8 and 12 weeks). Time-invariant (age, education, social support, optimism, trait anxiety, and number of previous courses of chemotherapy) and time-dependent (depressive symptoms, number of concurrent symptoms, perceived barriers to symptom management, currently on chemotherapy, and hospitalization) covariates were included in models for statistical adjustment. Estimated least squares means and their standard errors were reported at each time point. Missing data were handled through the linear mixed

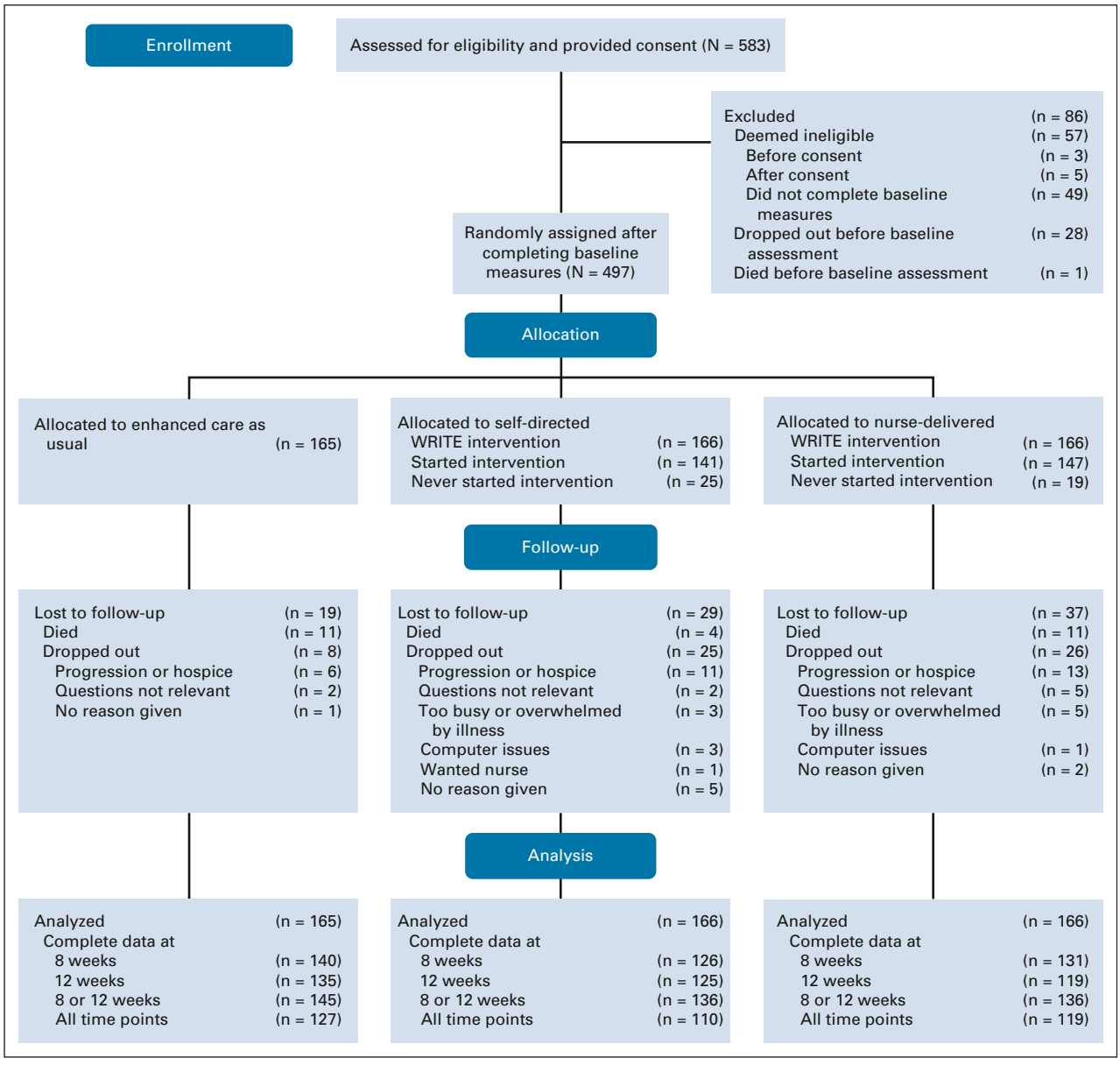

FIG 1. CONSORT diagram of participant progress through study.

modeling with outcome data assumed (and supported in preliminary analyses) to be missing at random. The significance level was set at $P < .025$ (two-tailed) for the two primary symptom outcomes to reduce risk of type-1 error.

RESULTS

Of the 583 patients consented after determination of eligibility, 497 (85.2%) completed BL measures within the 28 days required for participation and were randomly assigned (Nurse-WRITE: n = 166, SD-WRITE: n = 166, EUC: n = 165). Of these, 392 (78.9%) and 375 (75.5%) completed 8-week and 12-week follow-up assessments, respectively (Fig 1, CONSORT diagram).

See Table 2 for participant sociodemographic and clinical characteristics. Participants reported 14.2 (standard deviation [SD] = 4.9) concurrent symptoms at entry. Fatigue (n = 259; 52.1%), constipation (n = 125; 25.2%), and peripheral neuropathy (n = 124; 24.9%) were most common target symptoms for intervention. Most (85%) were receiving chemotherapy; 58.8% had received three or more previous chemotherapy regimens. No group differences were noted at BL ($P \geq .05$) for sociodemographic and clinical characteristics or covariates.

Participant Engagement

Sixty-nine percent of Nurse-WRITE and 77% of SD-WRITE participants completed a Symptom Care Plan for at least one target symptom. SD-WRITE participants completed the full intervention for 1.6 (SD = 1.7) symptoms; Nurse-WRITE participants completed the intervention for 1.0 (SD = 0.95) symptoms. Nurse-WRITE participants posted to the message board an average of 11.5 (median = 9; range, 0-47) times.

TABLE 2. Baseline Sociodemographic and Clinical Characteristics for all Participants (N = 497)

Characteristic	Mean (SD)	Range
Age, years	59.3 (9.2)	24-90
Formal education, years	14.7 (2.7)	10-22
Time since diagnosis, months (median = 37)	51.1 (42.1)	7-303
Previous cycles of chemotherapy, No. (median = 14)	16.0 (9.4)	1-62
Covariates		
Optimism	16.96 (3.84)	0-32
Trait anxiety	35.85 (22.96)	20-80
Social support	41.81 (5.95)	12-48
Symptom management barriers	4.20 (2.61)	0-16
Depressive symptoms	8.22 (5.23)	0-30

Characteristic	No. (%)
Non-Hispanic White	455 (91.5)
Annual household income < $30,000 USD	102 (22.0)
Somewhat or extremely difficult to pay for basic needs	187 (37.9)
Have received ≥ 3 previous chemotherapy regimens	295 (59.4)
Currently receiving chemotherapy	420 (85.2)

Abbreviations: SD, standard deviation; USD, US dollars.

Primary Outcomes

Target symptom burden. At BL, target symptom burden scores were comparable across groups ($P = .42$) and scores significantly decreased across all three groups from BL to 8 weeks (mean change = –1.002, SE = 0.063, $P < .001$) and BL to 12 weeks (mean change = –1.266, SE = 0.067, $P < .001$) (Table 3 and Fig 2A). No group by time interactions ($P = .18$) or group main effects ($P = .24$) were identified.

Symptom controllability. Target symptom controllability did not differ at BL among the three groups ($P = .58$). There was a significant group by time interaction (F = 4.76; $P < .001$) where both WRITE groups were superior to the EUC group (Table 3 and Fig 2B). Nurse-WRITE and SD-WRITE groups showed significant symptom controllability increases from BL to 8 weeks (Nurse-WRITE: mean change = 0.234, SE = 0.046, $P < .001$; SD-WRITE: mean change = 0.180, SE = 0.048, $P < .001$) and BL to 12 weeks (Nurse-WRITE: mean change = 0.215, SE = 0.052, $P < .001$; SD-WRITE: mean change = 0.162, SE = 0.053, $P = .002$). No significant changes over time ($P \geq .05$) were seen in EUC group.

QOL. There were no BL differences in QOL total scores among the groups ($P = .44$). A significant time effect was found for QOL (F = 9.48; $P < .001$), with scores increasing from BL to 8 weeks (mean change = 2.145, SE = 0.572, $P < .001$) and from BL to 12 weeks (mean change = 2.898, SE = 0.722, $P < .001$) in all groups. There were no significant group by time interactions ($P = .83$) or group main effects ($P = .24$) for QOL (Table 3 and Fig 2C).

DISCUSSION

In this multisite randomized controlled trial, the web-based WRITE Symptoms interventions, regardless of delivery method, improved participants' sense of control over their symptoms from BL to 8 and 12 weeks compared with those in EUC. These findings add to the literature on the potential benefits of web-based cancer-related symptom management to supplement in person clinical support. Both interventions included critical elements from the literature: symptom monitoring; facilitated communication with providers, evidence-based education to support symptom communication with providers, adherence to provider recommended pharmacologic interventions, and self-care strategies; and symptom management problem-solving and supported review and modification.[13] Unexpectedly, the higher intensity and individualized Nurse-WRITE was not superior to the computer-mediated SD-WRITE in exploratory analyses. In addition, participants in Self-WRITE were able to complete the intervention for more symptoms than were participants in Nurse-WRITE. Given the demonstrated benefit, its efficiency for both patients and clinicians, and the existing content and infrastructure, the SD-WRITE

TABLE 3. Descriptive Statistics (least squares means and SEs) and Test Statistics From Linear Mixed Modeling With Covariate Adjustment[a]

Outcome	Group				Test Statistics, *P* values
	ND WRITE, Mean (SE)	SD WRITE, Mean (SE)	EUC, Mean (SE)	Total, Mean (SE)	
SRQ-Burden Composite, weeks					
BL	5.18 (0.13)	5.26 (0.14)	5.21 (0.13)	5.22 (0.10)	F(group) = 1.75, .18
8	4.15 (0.14)	4.37 (0.14)	4.12 (0.14)	4.21 (0.10)	F(time) = 186.61, < .001
12	3.79 (0.14)	4.20 (0.15)	3.86 (0.14)	3.95 (0.10)	F(G × T) = 1.39, .24
Total	4.37 (0.12)	4.61 (0.13)	4.40 (0.13)		
SRQ-Control, weeks					
BL	2.23 (0.06)	2.25 (0.06)	2.19 (0.06)	2.22 (0.04)	F(group) = 7.99, < .001
8	2.47 (0.06)	2.43 (0.06)	2.16 (0.06)	2.35 (0.04)	F(time) = 11.80, < .001
12	2.45 (0.06)	2.41 (0.07)	2.16 (0.06)	2.34 (0.05)	F(G × T) = 4.76, < .001
Total	2.38 (0.05)	2.36 (0.06)	2.17 (0.05)		
FACT-G, weeks					
BL	109.79 (1.31)	108.41 (1.31)	109.36 (1.27)	109.19 (0.98)	F(group) = 1.44, .24
8	111.92 (1.29)	110.24 (1.36)	111.84 (1.32)	111.33 (0.95)	F(time) = 9.48, < .001
12	113.39 (1.34)	110.16 (1.40)	112.80 (1.35)	112.09 (0.98)	F(G × T) = 0.37, .83
Total	111.67 (1.15)	109.60 (1.19)	111.33 (1.16)		

Abbreviations: BL, baseline; CES-D, Center for Epidemiological Studies–Depression; EUC, Enhanced Usual Care; FACT-G, Functional Assessment of Cancer Therapy-General; LOT-R, Revised Life Orientation Test; ND, nurse-delivered; SD, self-directed; SRQ, Symptom Representation Questionnaire; STAI, State-Trait Anxiety Inventory.

[a]Linear mixed models included the following as covariates: STAI trait anxiety, CES-D depressive symptoms, LOT-R optimism, social support, age, years of education, perceived barriers to symptom management, symptom count, total courses of chemotherapy (baseline), receipt of chemotherapy during previous assessment period, and hospital stay.

intervention appears to be a scalable intervention with potential for testing in cancer care delivery.

Unexpectedly, the WRITE Symptoms interventions did not improve symptom burden or QOL compared with ECAU. A possible explanation for symptom burden may be in the highly variable nature of symptoms in recurrent cancer. Although symptom burden captures the current impact of symptoms, symptom controllability reflects positive expectancies in one's ability to control symptoms. In situations where experiences change from day to day, positive expectations for control may be important in predicting coping efforts and downstream outcomes such as QOL. Future studies should evaluate the temporal relationships between symptom controllability, symptom burden, use of symptom management strategies, and QOL outcomes.

Symptom burden and QOL improved over time for participants across the three groups. This finding is notable, given that multiple studies in this patient population demonstrate stable or gradual worsening of symptom burden and QOL over time that improves only after stopping therapy.[3,40] Improvements in symptom burden and QOL in the EUC group were unexpected and may have blunted the observed benefits of the WRITE interventions.

Although the lack of a true *usual care* group precludes inferences of efficacy, the EUC protocol appeared to be an active, low-dose intervention, containing elements consistent with other systematic symptom-monitoring interventions with demonstrated efficacy.[11,12]Further research is needed to identify whether the beneficial effects of symptom monitoring occur primarily through changes in patients' awareness and behaviors, changes in clinician behavior, or a combination of the two.

Our focus on patients with recurrent ovarian cancer was justified because of high symptom burden in this population. However, this decision may have dampened the effect of the interventions as these are expert patients with established symptom management patterns and expectations. Many participants noted their expertise and suggested interventions be targeted earlier in their illness. Furthermore, 6% of participants were admitted to hospice during the 12-week study period, suggesting that their symptoms were urgent and arguably not appropriate for a self-management intervention.

We made the difficult decision not to anchor enrollment and assessments to diagnosis of a new recurrence. This decision enhanced generalizability of study findings but may have increased random error and reduced power to detect significant group differences in outcomes.

The desire to create an asynchronous intervention and to leverage the cathartic and problem-solving value of expressive writing[41,42] extended the time necessary to generate an individualized symptom care plan for patients in the Nurse-WRITE group. Conversely, in SD-WRITE,

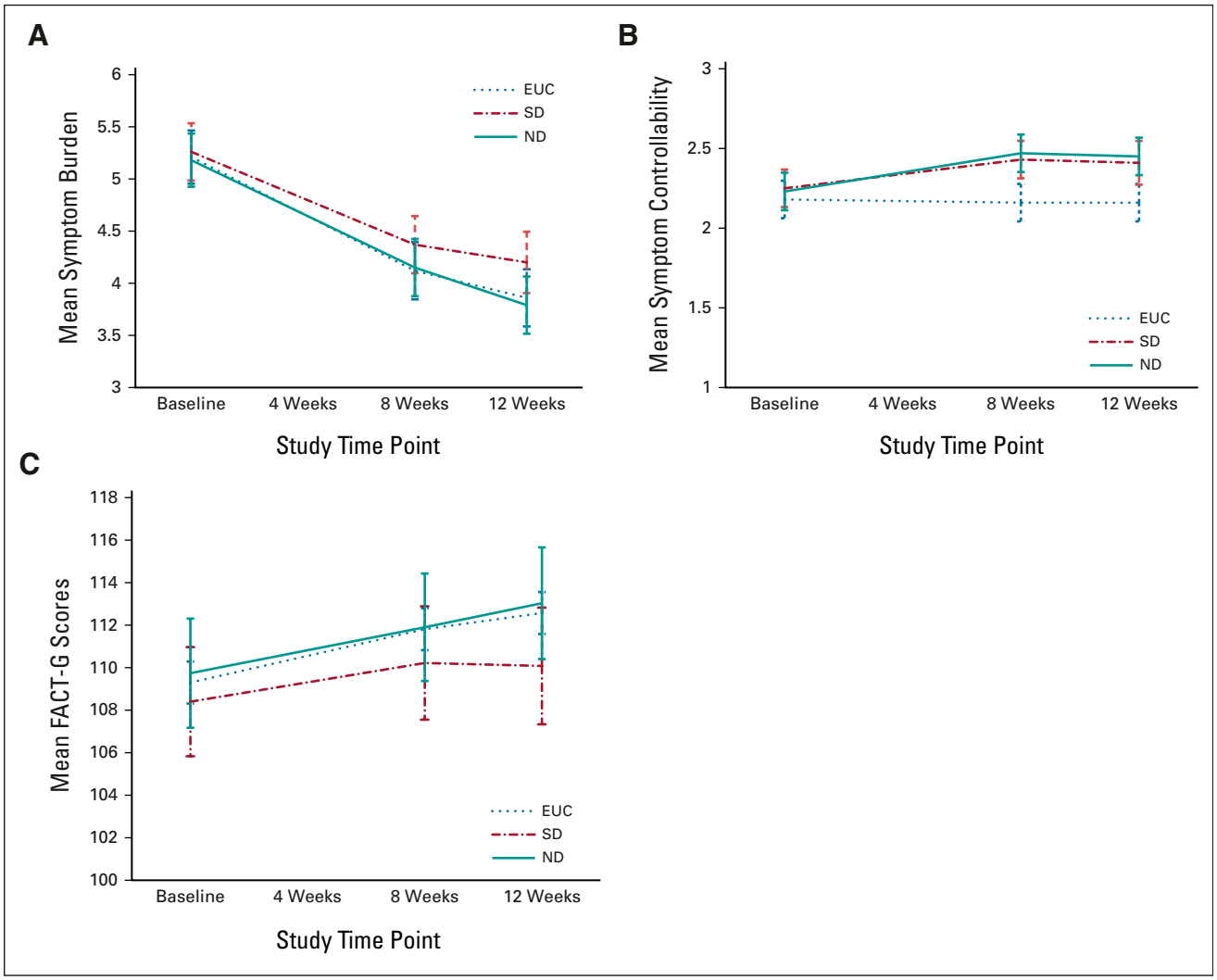

FIG 2. (A) Changes in symptom burden with 95% CI over time by group assignment. (B) Changes in symptom controllability with 95% CI over time by group assignment. (C) Changes in quality of life with 95% CI over time by group assignment. EUC, enhanced usual care; ND, nurse-delivered; SD, self-directed.

participants could progress through assessment to care plan development in 20-30 minutes.

Additional analyses are underway to better understand the perceived effectiveness of specific symptom management strategies used during the intervention. Future research should also consider which patients are most likely to benefit from self-management interventions. Patients with few or mild symptoms may be less motivated to engage in symptom management interventions. Conversely, participants with high symptom burden had difficulty engaging in the interventions. Hospitalizations, ER visits, disease progression, and hospice admissions were common barriers to participation. Future research should focus on ways to reduce the work of symptom management for highly burdened patients.

In conclusion, Nurse- and SD-WRITE were statistically superior to EUC in symptom control. Given increased efficiency of SD-WRITE for patients and providers as well as scalable content and infrastructure, an implementation study of SD-WRITE is warranted. Future research should evaluate whether a tiered WRITE Symptoms (progression from the low intensity EUC to SD- to Nurse-WRITE) on the basis of patient preference and/or risk assessment would be a cost-effective approach to strengthening WRITE Symptoms.

AFFILIATIONS

[1]University of Pittsburgh School of Nursing, Pittsburgh, PA
[2]Magee Womens Hospital of UPMC Hillman Cancer Center, Pittsburgh, PA
[3]Medicine and Public Health, University of California, Irvine, CA
[4]University of Wisconsin, Madison, WI
[5]University of Pittsburgh School of Computing and Information, Pittsburgh, PA
[6]Abington Memorial Hospital, Gynecologic Oncology Institute, Abington, PA
[7]Stephenson Cancer Center Gynecologic Cancers Clinic, University of Oklahoma Health Sciences Center, Oklahoma City, OK

[8]Minnesota Oncology, Edina, MN
[9]Washington University School of Medicine, Siteman Cancer Center, St Louis, MO
[10]Obstetrics and Gynecology, Cleveland Clinic, Cleveland, OH
[11]Gynecologic Oncology, UNM School of Medicine, University of New Mexico Albuquerque, NM
[12]Gynecology Oncology, VCU Medical Center North Hospital, Richmond, VA

CORRESPONDING AUTHOR

Heidi S. Donovan, PhD, RN, University of Pittsburgh School of Nursing, 415 VB, 3500 Victoria St, Pittsburgh, PA 15261; e-mail: donovanh@pitt.edu.

PRIOR PRESENTATION

Presented in abstract form at the Annual Meeting of the Society of Gynecologic Oncology, National Harbor, MD, March 12-15, 2017.

SUPPORT

Supported by a grant from the National Institutes of Health, National Institute of Nursing Research NIH-NINR R01NR010735-NRG Oncology GOG-259 (H.S.D., Study Chair) as well as NIH-NCI grants to NRG Oncology (U10CA180822), NRG Operations (U10CA180868), and UG1CA189867 (NCORP).

CLINICAL TRIAL INFORMATION

NCT00958698

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.00656.

DATA SHARING STATEMENT

All data elements of the individual participants that are required to reproduce results reported in this article (text, tables, figures, supplemental material) after de-identification will be made available upon request. Data will comply with rules and regulations of the NCTN Data Archive. The protocol document and data dictionary will also be made available. Data will be available through the National Institutes of Health, National Cancer Institute, NCTN/NCORP Data Archive (https://nctn-data-archive.nci.nih.gov/) within 6 months of publication of this article. Data will be made available to researchers with an approved Data Use Agreement who wish to analyze the data in secondary studies to enhance the public health benefit of the original work. Data requesters must sign a Data Use Agreement before being able to download data for a given data request. Please see NRG Data Sharing Policy at https://www.nrgoncology.org/Portals/0/About%20Us/Policies/NRG%20Oncology%20Data%20Sharing%20Policy.pdf. Researchers must adhere to all terms of access in the Data Use Agreement. The Data Use Agreement is in effect for up to 3 years. An extension can be pursued or the data in all forms must be destroyed.

AUTHOR CONTRIBUTIONS

Conception and design: Heidi S. Donovan, Susan M. Sereika, Lari B. Wenzel, Robert P. Edwards, Judith E. Knapp, Susan H. Hughes, Michael B. Spring, Susan Nolte, Sandra E. Ward
Financial support: Heidi S. Donovan
Administrative support: Heidi S. Donovan, Robert P. Edwards, David G. Mutch
Provision of study material or patients: Heidi S. Donovan, Susan H. Hughes, Susan Nolte, Lisa M. Landrum, David G. Mutch, Robert L. DeBernardo, Carolyn Y. Muller, Stephanie A. Sullivan
Collection and assembly of data: Heidi S. Donovan, Robert P. Edwards, Judith E. Knapp, Susan H. Hughes, Mary C. Roberge, Teresa H. Thomas, Michael B. Spring, Lisa M. Landrum, Carolyn Y. Muller
Data analysis and interpretation: Heidi S. Donovan, Susan M. Sereika, Lari B. Wenzel, Robert P. Edwards, Susan H. Hughes, Teresa H. Thomas, A. Catherine Casey, Robert L. DeBernardo, Stephanie A Sullivan, Sandra E. Ward
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

Additionally, WRITE Symptoms is licensed under the Creative Commons Attribution-Noncommercial-Share Alike 3.0 United States License. To view a copy of this license, visit http://creativecommons.org/licenses/by-nc-sa/3.0/us/ or send a letter to Creative Commons, San Francisco, CA. The authors are deeply indebted to all of the women who participated in this trial. They are grateful to the nurses of the GOG-nursing committee, and each clinical site for championing this study. A special acknowledgment goes out to their website developers, Rajesh Babu and Arun Karthick, for their creativity and persistence in developing the complex features of the WRITE Symptoms web-based system.
The following NRG Oncology/Gynecologic Oncology Group member institutions participated in this study: University of Pittsburgh Cancer Institute; University of Oklahoma Health Sciences Center, Metro-Minnesota CCOP, Washington University School of Medicine, Northern Indiana Cancer Research Consortium, Case Western Reserve University, University of New Mexico, Virginia Commonwealth University, Fox Chase Cancer center, Saint Vincent Hospital, University of Minnesota Medical Center- Fairview, Wisconsin NCI Community Oncology Research Program, University of Wisconsin Hospital and Clinics, Wayne State University/Karmanos Cancer Institute, Walter Reed National Military Medical Center, University of Massachusetts Memorial Health Care, Carle Cancer Center, Fred Hutchinson Cancer Research Center, Mainline Health CCOP, University of Colorado Cancer Center-Anschutz Cancer Pavilion, Women and Infants Hospital, University of California at Los Angeles Health System, Kansas City CCOP, Cleveland Clinic Foundation, Central Illinois CCOP, Iowa-Wide Oncology Research Coalition NCORP, The Hospital of Central Connecticut, University of Iowa Hospitals and Clinics, Indiana University Hospital/Melvin and Bren Simon Cancer Center, University of Texas-Galveston, Abington Memorial Hospital, Aurora Women's Pavilion of Aurora West Allis Medical Center, University of Hawaii, and William Beaumont Hospital.

REFERENCES

1. American Cancer Society: Cancer Facts and Figures 2021. Atlanta, GA, 2021. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf
2. Coleman RL, Fleming GF, Brady MF, et al: Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med 381:2403-2415, 2019
3. von Gruenigen VE, Huang HQ, Cella D, et al: Quality of life, symptoms and care needs in patients with persistent or recurrent platinum-resistant ovarian cancer: An NRG Oncology/Gynecologic Oncology Group study. Gynecol Oncol 150:119-126, 2018
4. Colombo N, Lorusso D, Scollo P: Impact of recurrence of ovarian cancer on quality of life and outlook for the future. Int J Gynecol Cancer 27:1134-1140, 2017
5. Aghajanian C, Goff B, Nycum LR, et al: Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol 139:10-16, 2015

6. Donovan HS, Ward S, Sherwood P, et al: Evaluation of the symptom representation questionnaire (SRQ) for assessing cancer-related symptoms. J Pain Symptom Manage 35:242-257, 2008
7. National Academies of Sciences, Engineering and Medicine: Ovarian Cancers: Evolving Paradigms in Research and Care. Washington, DC, The National Academies Press, 2016. www.nas.edu/OvarianCancers
8. Kohl LFM, Crutzen R, de Vries NK: Online prevention aimed at lifestyle behaviors: A systematic review of reviews. J Med Internet Res 15:e146, 2013
9. Ammann R, Vandelanotte C, de Vries H, et al: Can a website-delivered computer-tailored physical activity intervention be acceptable, usable, and effective for older people? Health Educ Behav 40:160-170, 2013
10. Latulippe K, Hamel C, Giroux D: Social health inequalities and eHealth: A literature review with qualitative synthesis of theoretical and empirical studies. J Med Internet Res 19:e136, 2017
11. Basch E, Kris MG, Scher HI, et al: Symptom monitoring with patient-reported outcomes during routine cancer treatment: A randomized controlled trial. J Clin Oncol 34:557-565, 2016. [Erratum: J Clin Oncol 34:2198, 2016. Erratum: J Clin Oncol 37:528, 2019]
12. Basch E, Deal AM, Dueck AC, et al: Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. JAMA 318:197-198, 2017
13. Fridriksdottir N, Gunnarsdottir S, Zoëga S, et al: Effects of web-based interventions on cancer patients' symptoms: Review of randomized trials. Support Care Cancer 26:337-351, 2018
14. Wantland D, Portillo C, Holzemer W, et al: The effectiveness of web-based vs. non-web-based interventions: A meta-analysis of behavioral change outcomes. J Med Internet Res 6:E40, 2004
15. Donovan HS, Ward S: A representational approach to patient education. J Nurs Scholarsh 33:211-216, 2001
16. Donovan HS, Ward SE, Song M-K, et al: An update on the representational approach to patient education. J Nurs Scholarsh 39:259-265, 2007
17. Arida JA, Sherwood PR, Flannery M, et al: Representational approach: A conceptual framework to guide patient education research and practice. Oncol Nurs Forum 43:781-783, 2016
18. Leventhal H, Nerenz D, Steele D: Illness representations and coping with health threats, in Baum A, Singer J (eds): Handbook of Psychology and Health, Volume IV. New York, NY, Erlbaum, 1984, pp 221-252
19. Leventhal H, Diefenbach M: The active side of illness cognition, in Skelton J, Croyle R (eds): Mental Representation in Health and Illness. New York, NY, Springer-Verlag, 1991, pp 247-272
20. Hewson P, Thorley N: The conditions of conceptual change in the classroom. Int J Sci Educ 11:541-553, 1989
21. Posner GJ, Strike KA, Hewson PW, et al: Accommodation of a scientific conception: Toward a theory of conceptual change. Sci Educ 66:211-227, 1982
22. Hewson MG: Patient education through teaching for conceptual change. J Gen Intern Med 8:393-398, 1993
23. Donovan HS, Ward SE, Sereika SM, et al: Web-based symptom management for women with recurrent ovarian cancer: A pilot randomized controlled trial of the WRITE symptoms intervention. J Pain Symptom Manage 47:218-230, 2014
24. HS Donovan, R Babu, M Spring. Development and testing of the self-directed WRITE symptoms cancer symptom management module. Unpublished data cited in NIH/NINR010735: Web-based Cancer Symptom Control: Nurse-Guided vs. Self-Directed. 2008
25. Cella DF, Tulsky DS, Gray G, et al: The Functional Assessment of Cancer Therapy Scale: Development and validation of the general measure. J Clin Oncol 11: 570-579, 1993
26. Basen-Engquist K, Bodurka-Bevers D, Fitzgerald MA, et al: Reliability and validity of the functional assessment of cancer therapy–ovarian. J Clin Oncol 19: 1809-1817, 2001
27. Wenzel LB, Huang HQ, Armstrong DK, et al: Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: A Gynecologic Oncology Group study. J Clin Oncol 25:437-443, 2007
28. Scheier MF, Carver CS, Bridges MW: Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): A reevaluation of the life orientation test. J Pers Soc Psychol 67:1063-1078, 1994
29. Schou-Bredal I, Heir T, Skogstad L, et al: Population-based norms of the Life Orientation Test-Revised (LOT-R). Int J Clin Health Psychol 17:216-224, 2017
30. Spielberger CD, Gorsuch RL, Lushene R, et al: Manual for the State-Trait Anxiety Inventory. Palo Alto, CA, Consulting Psychologists Press, 1983
31. Julian LJ: Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Arthritis Care Res (Hoboken) 63:S467-S472, 2011 (suppl 11)
32. Merz EL, Roesch SC, Malcarne VL, et al: Validation of interpersonal support evaluation list-12 (ISEL-12) scores among English-and Spanish-Speaking Hispanics/Latinos from the HCHS/SOL sociocultural ancillary study. Psychol Assess 26:384-394, 2014
33. Wills TA, Shinar O: Measuring perceived and received social support, in Cohen S, Underwood LG, Gottlieb BH (eds): Social Support Measurement and Intervention: A Guide for Health and Social Scientists. Oxford, UK, Oxford University Press, 2000, pp 86-135
34. Cohen S, Mermelstein R, Kamarck T, et al: Measuring the functional components of social support, in Sarason IG, Sarason BR (eds): Social Support: Theory Research and Application. The Hague, the Netherlands, Martinus Nijhoff, 1985, pp 73-94
35. Gunnarsdottir S, Donovan HS, Serlin RC, et al: Patient-related barriers to pain management: The barriers questionnaire II (BQ-II). Pain 99:385-396, 2002
36. Passik SD, Kirsh KL, Donaghy K, et al: Patient-related barriers to fatigue communication: Initial validation of the fatigue management barriers questionnaire. J Pain Symptom Manage 24:481-493, 2002
37. Ward SE, Wang KK, Serlin RC, et al: A randomized trial of a tailored barriers intervention for Cancer Information Service (CIS) callers in pain. Pain 144:49-56, 2009
38. Hann D, Winter K, Jacobsen P: Measurement of depressive symptoms in cancer patients: Evaluation of the center for epidemiological studies depression scale (CES-D). J Psychosom Res 46:437-443, 1999
39. Zhang W, O'Brien N, Forrest JI, et al: Validating a shortened depression scale (10 item CES-D) among HIV-Positive people in British Columbia, Canada. PLoS One 7:e40793, 2012
40. Friedlander ML, Stockler M, O'Connell R, et al: Symptom burden and outcomes of patients with platinum resistant/refractory recurrent ovarian cancer a reality check: Results of stage 1 of the gynecologic cancer intergroup symptom benefit study. Int J Gynecol Cancer 24:857-864, 2014
41. Cameron LD, Nicholls G: Expression of stressful experiences through writing: Effects of a self-regulation manipulation for pessimists and optimists. Health Psychol 17:84-92, 1998
42. Pennebaker JW: Writing about emotional experiences as a therapeutic process. Psychol Sci 8:162-166, 1997

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Effects of the WRITE Symptoms Interventions on Symptoms and Quality of Life Among Patients With Recurrent Ovarian Cancers: An NRG Oncology/GOG Study (GOG-0259)

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. 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 ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Lari B. Wenzel
Consulting or Advisory Role: Array BioPharma

Robert P. Edwards
Research Funding: Merck

Mary C. Roberge
Research Funding: Clovis Oncology (Inst)

Teresa H. Thomas
Consulting or Advisory Role: Healthline Media, Mashup Media

David G. Mutch
Consulting or Advisory Role: Lilly

Carolyn Y. Muller
Research Funding: AstraZeneca (Inst), Genmab (Inst), VBL Therapeutics (Inst), Roche/Genentech (Inst), TapImmune Inc (Inst), Linnaeus Therapeutics (Inst), Agenus (Inst), Incyte (Inst), Merck (Inst)
Patents, Royalties, Other Intellectual Property: Have a pending patent on the cancer use for R-ketorolac—not yet its own new drug (Inst)
Other Relationship: NCI, Department of Defense

No other potential conflicts of interest were reported.