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An Online Randomized Controlled Trial, with or without Problem Solving Treatment, for Long-Term Cancer Survivors after Hematopoietic Cell Transplantation

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Abstract

Purpose—This randomized controlled trial examines the efficacy of *INSPIRE*, an INternet-based Survivorship Program with Information and REsources, with or without Problem-Solving Treatment (PST) telehealth calls, for survivors after hematopoietic cell transplantation (HCT).

Methods—All adult survivors who met eligibility criteria, were approached for consent. Participants completed patient-reported outcomes at baseline and 6 months. Those with baseline impaired scores on one or more of the outcomes were randomized to *INSPIRE*, *INSPIRE*+PST, or control with delayed *INSPIRE* access. Outcomes included Cancer and Treatment Distress, Symptom Checklist-90-R Depression, and Fatigue Symptom Inventory. Planned analyses compared arms for mean change in aggregated impaired outcomes and for proportion of participants improved on each outcome.

Results—Of 1306 eligible HCT recipients, 755 (58%) participated, and 344 (45%) had one or more impaired scores at baseline. We found no reduction in aggregated outcomes for either intervention ($P>0.3$). In analyses of individual outcomes, participants randomized to *INSPIRE* +PST were more likely to improve in distress than controls (45% vs. 20%, RR 2.3, CI 1.0, 5.1); those randomized to *INSPIRE* alone were marginally more likely to improve in distress (40% vs. 20%, RR 2.0, CI 0.9, 4.5).

Conclusions—The *INSPIRE* online intervention demonstrated a marginal benefit for distress that improved with the addition of telehealth PST, particularly for those who viewed the website or were age 40 or older.

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Conflict of Interest Disclosures: none

Implications for Cancer Survivors—Online and telehealth programs such as *INSPIRE* offer opportunities to enhance HCT survivorship outcomes, particularly for mood, though methods would benefit from strategies to improve efficacy.

Introduction

Hematopoietic cell transplantation (HCT) is complicated by some of the highest rates of late effects and late mortality of any current cancer treatment [1-5]. Recovery can be lengthy, with an estimated 63% of survivors returning to pretransplant levels of physical and psychological function after 5 years [6, 7]. Many HCT survivors continue to report depression, cancer related distress and fatigue compared with their siblings or age-matched norms.[6, 8-10] The cumulative incidence of one or more major physical or mental late effects 5 years after transplant is estimated at 45% and 79% for autologous and allogeneic HCT recipients respectively [11]. Emotional distress is far more prevalent than clinical depression after HCT, with the distress prevalence estimated at 43%, and moderate to severe depressive symptoms found in 13-15% of long-term HCT survivors [12, 10, 13, 14].

Health care delivery and psychosocial interventions for HCT survivors are challenging due to the distance most live from transplant centers, their varying needs, and the lack of standard follow-up care. Few interventions have been tested to meet their health requirements. One randomized controlled trial (RCT) with 1-3 year survivors found that 10 phone-delivered sessions of cognitive behavioral treatment reduced distress, depressive and post-traumatic stress symptoms with effects sustained for 12 months [15]. A second trial comparing in-person, mindfulness-based training to a supportive telephone consultation found that mindfulness improved quality of life, depression and anxiety but not fatigue, and did not have sustained effects [16]. Both of these intensive interventions required relatively high levels of expertise, limiting their reach.

Online programs are an attractive option for HCT survivors who frequently use the internet for information [17-20]. A few online RCTs for non-HCT cancer patients have been efficacious when targeting depressive symptoms, [21-24] distress, [25] sexual function, [26, 27] fear of recurrence, [28] fatigue, [24, 29] insomnia, [30] physical function [31] or physical activity [32]. However, effect sizes of internet RCTs are generally small or not significant as confirmed by systematic reviews [33-35]. Most studies report feasibility and acceptability rather than outcomes [36-48].

Telehealth models of care delivery also have advantages for HCT survivors who live far from post-transplant expertise [15]. We effectively targeted fatigue and distress with a psychoeducational intervention using telehealth ‘booster’ calls after onsite workshops in the first year after transplant [49]. Problem-Solving Treatment (PST) delivered by phone has shown promise for treating depression in breast cancer survivors and other populations [50, 51]. PST is a brief intervention that requires less advanced training than cognitive behavioral therapy [52]. Since online interventions are not consistently effective, we predicted that PST could boost efficacy beyond an online intervention alone for HCT survivors.

The aim of the *INSPIRE* RCT was to determine the efficacy of an online program alone or in combination with telehealth-delivered PST to improve the primary outcomes of depression, cancer-related distress, fatigue and physical dysfunction in adult, long-term HCT survivors with impaired symptoms at baseline assessment. We have previously described the development and reach of the *INSPIRE* (INternet-based Survivorship Program with Information and REsources) online intervention.[53] For the RCT, we hypothesized that HCT survivors with impaired target symptoms who were randomized to the *INSPIRE* intervention with or without PST would have more improved aggregated primary outcomes at the 6-month assessment compared to controls. Additional hypotheses predicted higher rates of improvement in the individual outcomes for the intervention arms compared with controls, and improved response rates to the intervention for participants who were under age 40 and had higher levels of engagement as measured by pages viewed on the *INSPIRE* site.

Methods

Participants

All HCT survivors treated at a single transplant center were approached if they met the following criteria: age18 or older, 3-18 years since most recent transplant, U.S. or Canadian residents, with internet and email access, and adequate English to complete the baseline assessment. Exclusion criteria included recurrence or subsequent malignancy requiring treatment more than surgical excision during the two years prior to enrollment. Participants reporting suicidal ideation or severe depression were contacted by phone to ensure their safety and access to treatment in their communities. They were not randomized but were given access to the *INSPIRE* site.

Procedure

The RCT was registered with ClinicalTrials.gov (NCT00799461). All procedures were approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center (Fred Hutch). Eligible survivors were sent up to three letters of approach, with follow-up calls for non-responders. Interested survivors received a link to the website for registration, consent, and completion of patient-reported outcomes (PRO). Participants were assigned to group 1 if their scores were impaired on depression, distress and/or fatigue measures, and were included in the primary analyses. Randomization was carried out using an adaptive randomization algorithm and was stratified on gender, stem cell source (autologous versus allogeneic), race/ethnicity (Non-Caucasian or Hispanic vs. white and Non-Hispanic), and transplant institution (Fred Hutch vs. non-Fred Hutch). Group 1 participants were randomized to one of three arms: *INSPIRE* online access plus PST calls (*INSPIRE*+PST), *INSPIRE* access alone, or delayed *INSPIRE* access after 6-month assessment (control). Participants were assigned to group 0 if they had no impaired scores on distress, depression or fatigue measures. Group 0 participants were randomized to *INSPIRE* access or control and were not included in the primary analyses. After 6 months, participants completed the outcome assessment, after which those in the control group were given access to *INSPIRE*.

Intervention: INSPIRE—*INSPIRE* site content and study reach have been previously described. [53] Briefly, the *INSPIRE* site consisted of seven levels: 1) A greeting home page tailored to each participant, with links to sections identified as impaired at baseline. 2) Three main topics: lifting mood, reducing fatigue, and boosting health. 3) Self-care tips and tools for common complications. 4) Tailored health care guidelines, which were also mailed to survivors to take to providers or use for self-care. 5) A forum for posting survivor experiences and input. 6) Annotated national and local resources. 7) A comment box for sending secure messages to study staff. The entire site was available to intervention arm participants throughout the study.

Intervention: PST Calls—PST focused on problems and goal setting toward solutions as specified by the participant during the first call with the clinicians who were PhD psychologists (SA, JR, JY) trained and certified in PST by Dr. Mark Hegel who developed the method. [51] The first session lasted an hour and explained PST, collected an initial problem list, and applied the PST process to one problem. Subsequent sessions (3 to 7 depending on need) lasted 30 minutes and applied PST to one problem per session. PST sessions were about two weeks apart to give participants time to work on goals.

Measures

Sources of data included PST audiotapes, medical records, PRO, and *INSPIRE* page views tracked by date and time.

PST Process and Fidelity—All PST sessions were audiotaped after consent. Dr. Hegel reviewed 36% of the tapes and rated fidelity to the treatment manual on 7 elements and global fidelity, with each item rated from 0=very poor to 5=very good. Clinicians received feedback and reviews of fidelity in monthly phone supervision by Dr. Hegel. A minimum dose of 4 sessions was required to indicate PST completion [51].

Medical and Sociodemographic Data—Medical records provided diagnosis, transplant details, years post-transplant, history of relapse, and chronic graft versus host disease (cGVHD). Medicare and Medicaid categorization of zip codes provided coding for rural versus urban residence (http://www.cms.hhs.gov/AmbulanceFeeSchedule/).

Patient-Reported Outcomes (PRO)—The PRO included demographic information, computer experience, and cGVHD treatment. Outcomes included Cancer and Treatment Distress (CTXD), Symptom Checklist-90-R depression scale (SCL-90-R), Short Form 36 Health Survey (SF-36), and Fatigue Symptom Inventory (FSI). The CTXD is a 22-item measure of distress or worry related to cancer events, with a mean score >1.10 indicating elevated distress [54]. The measure has been tested with HCT survivors as a predictor of health outcomes, and has been used in several RCTs [54, 6, 55-57]. The SCL-90-R depression scale is a widely used, psychiatrically validated, 20-item measure of depressive symptoms [58]. A mean score >1.0 indicates depressive symptoms of mild or greater severity. The SF-36 measures health-related quality of life across eight dimensions [59]. The physical function subscale used as an outcome has a standardized t-score of 50 and standard deviation of 10; a cut point of <40 indicates impaired physical function. The FSI is validated

for use in cancer populations and has 13 items, with a mean score >4.7 indicating elevated fatigue [60, 61].

Statistical Analysis

The primary endpoint defined at study inception was the aggregate number of targeted problems with impaired scores at the 6-month endpoint for participants in group 1, including cancer and treatment distress, depressive symptoms, physical dysfunction and fatigue, resulting in a possible range of 0-4. To account for variability in baseline aggregate numbers of conditions, the analytic outcome used for primary analyses was the change in aggregate number of conditions between baseline and six months. The sample size was selected to allow more than 90% power to detect effect sizes in aggregate numbers of conditions of 0.5 standard deviation difference between each intervention and control arm assuming a type I overall error rate of 0.05 with Bonferroni adjustment applied to allow for two pairwise comparisons between study arms (each with 0.025 two-sided significance level). Balance between study arms was evaluated for key factors that may influence outcomes such as age, years since transplant, type of transplant (autologous or allogeneic), race/ethnicity, gender, education, income, cancer diagnosis and rural vs. urban residence as well as subjects' baseline aggregate number of targeted problems. Planned secondary analyses included subset analyses of each endpoint among participants meeting eligibility for randomization due to that endpoint (e.g. distress, depression, fatigue and physical functioning). For each of these subgroups, the relevant binary outcome of success was defined (e.g. not impaired on distress), and the proportion of participants meeting that criterion at the 6-month time point was compared between study arms. Since selection of subgroups could result in imbalances between study arms, we carefully evaluated balance between arms for each subset and found good balance between arms in all subsets. Additional exploratory analyses examined the impact of two hypothesized modifying factors on intervention efficacy, specifically engagement indicated by viewing two or more website pages, i.e., views beyond the landing page, and current age <40 or 40+ years. We evaluated interactions between these factors and the study arms. Since baseline characteristics were well balanced between study arms, primary analytic comparisons were univariate, using t-tests to compare mean change in aggregate counts between 6 month and baseline values. Chi-square tests were used to compare proportions. Additional analyses evaluating the impact of patient characteristics on relative risk estimates were carried out using generalized linear models with a log-link function and Poisson errors [62].

Results

Characteristics of the Cohort

Of the 1755 HCT survivors approached who met initial eligibility criteria, 1306 met full eligibility (Figure 1), and 755 (58% of eligible) consented, completed baseline assessment. Of the 755, 45% (n=344) met impaired symptom criteria for assignment to group 1 and randomization, while 411 did not and were assigned to group 0. Seven participants in group 1 were prospectively designated for ‘run-in’ testing for *INSPIRE*+PST (two completed PST cases per clinician) and therefore were not included in analyses.

Participants, compared with those eligible but not enrolled, were more likely to be over age 40, white, treated for acute leukemia or myelodysplasia, less than 10 years after HCT, and with a history of cGVHD (all $P<.05$, Table 1). Randomized arms in group 1 were comparable in demographic and clinical characteristics, with the exception that the control arm was more likely to have no current cGVHD ($P=.02$, Table 2). Group 1 participants were 18 to 76 years (mean 51, SD 12), 53% male, and over 90% white and non-Latino (Table 2). A majority, 68%, were less than 10 years from first transplant. A quarter of allogeneic survivors were in active treatment for cGVHD (n=59, 24%). Within group 1, impaired scores were reported for distress by 36% (n=120), for depression symptoms by 40% (n=134), for fatigue by 31% (n=106), and for physical dysfunction by 31% (n=104). Depression and distress were correlated (r=0.77) as were distress and fatigue (r=0.56) and fatigue and physical function (r=-0.47).

Process Measures: INSPIRE Page Views, PST Calls, and PST Fidelity

For the n=222 given immediate access to *INSPIRE* and in analyses (not including the seven run-in cases), median number of page views was 9, with an interquartile range of 0-23, and a full range of 0-179. A third (32%, n=71) viewed no pages or only visited the home page of the site. The intervention arms did not differ in page views ($P=.67$, Table 2). Among *INSPIRE*+PST participants, n=15 (14%) declined PST calls but continued with *INSPIRE* online; n=19 (18%) started but did not complete PST. On average, participants received 4.5 calls (SD=2.8). Mean ratings of clinician fidelity to the PST manual ranged from 4.2-4.8; global ratings had a mean score of 4.0 (SD=1.0), equivalent to “good.”

Primary Outcome Analysis of the Aggregated Outcome

There were no differences in the mean change in aggregated endpoint score from baseline to six months between the three study arms (all $P>0.3$). Mean (Standard Deviation [SD]) change in aggregate endpoints from baseline to 6 months were 0.30 (1.23), 0.38 (1.28) and 0.29 (1.15) for the *INSPIRE+PST*, *INSPIRE* alone and control arms, respectively.

In the primary analysis and secondary analyses below we evaluated adjusted analyses for the aggregate score and for individual outcomes, and found no factors that affected point estimates between study arms. Inclusion of other factors reduced power and decreased precision of the estimates. Factors considered included: current age (<40 vs. 40+ years), education (<4 vs. 4+ years of college), gender, rural/urban residence, autologous versus allogeneic HCT, years since diagnosis, cGVHD, and within the intervention arms the number of pages of *INSPIRE* visited.

Planned Secondary Analyses of Individual Outcomes

Table 3 provides results of analyses comparing the proportion of survivors achieving a successful outcome for each measure among participants with impaired scores for that outcome at baseline. Compared to controls, *INSPIRE*+PST recipients demonstrated improvement in distress (RR=2.3, CI 1.0, 5.1, $P=.032$); *INSPIRE* alone participants demonstrated a trend toward improvement (RR=2.0, CI 0.9, 4.5, $P=.075$). We found no differences between intervention arms and controls in rates of change in depressive symptoms, fatigue or physical functioning (RR's 0.6 to 1.4).

Although the study had limited power to assess interactions, we explored whether selected subgroups improved more in distress or depression within the arms. In the *INSPIRE* arm, those with impaired depression scores at baseline who viewed two or more pages of the site had improved depression compared to controls (60% vs. 36%, RR=1.7, CI 1.0, 2.8, *P*=.047); distress was marginally improved for this subgroup: (40% vs. 20%, RR=2.0, CI 0.9, 4.6, P=.091). In the *INSPIRE*+PST arm, those who viewed two or more pages had improved distress compared to controls (42% vs. 20%, RR=2.7, CI 1.2, 6.1, P=.009), but not improved depression. Relatively few participants had fewer than two page views, which was set as a cut-point indicative of views of the website beyond the landing page. However, in the *INSPIRE* arm those with two or more page views had a marginally higher rate of improvement in depression (RR=2.7, CI 0.8, 9.5, *P*=.065) compared with those with one or no page views. There were no age differences across arms in improvement in depression. However, contrary to our hypothesis, for survivors age 40 or older rather than under age 40, distress was more likely to improve for those in the *INSPIRE+PST* arm (RR=4.2, CI 1.4, 12.8, *P*=.003) and the *INSPIRE* arm (RR=3.9, CI 1.3, 12.0, *P* =.006) compared to controls. Although there were few participants below age 40, we found significant interactions for distress outcomes between age and each intervention arm (*INSPIRE*+PST *P*=.025; *INSPIRE* *P*=.009), indicating that the interventions were potentially more effective among survivors over age 40 than under age 40.

Discussion

Online programs and telehealth calls provide resource-conserving access to survivorship knowledge and tools for HCT recipients who may live far from their transplant centers. This RCT of an internet and telehealth intervention addressing distress, depression and fatigue demonstrated a high enrollment rate (58%) relative to other internet-based RCTs. [53, 63] Although we found no differences between the study arms on the primary endpoint of aggregated outcomes, the secondary endpoint of distress improved significantly for those in the *INSPIRE*+PST arm at six months, with a more modest effect for *INSPIRE* alone. As hypothesized, survivors receiving *INSPIRE* alone who viewed two or more pages were more likely to report improved depression and a trend toward improved distress. Conversely, those receiving *INSPIRE*+PST who viewed two or more pages reported improved distress but not depressive symptoms. Of note, distress and depression were strongly correlated (r=0.77). Contrary to hypothesis, survivors 40 or older, rather than under age 40, also had improved distress with either intervention.

Online interventions for chronic diseases and cancer have proliferated although with mixed success [64, 34, 65]. Challenges include recruiting those with more severe chronic symptoms to enroll, [66, 67] and maintaining engagement for those who enroll [68]. Effect sizes are often modest at best since many of those who remain engaged with the program are already doing well, and improvement is therefore difficult to measure [69]. Nonetheless, cancer survivors, including after HCT, remain interested in using these modalities [70, 71].

High attrition rates are major reasons for reduced effect sizes of online interventions compared with face-to-face treatments [72]. Our attrition rate of 32% is consistent with other oncology online studies that include one for fatigue that had a 38% dropout and another for

coping skills in cancer survivors that had a 32% attrition rate [29, 73]. It is also worth noting that a meta-analysis of dropouts from in-person psychotherapy for anxiety is 17%, with no definable modifiers based on patient, therapist, or treatment variables and can range up to at least 38% for some in-person treatments [74, 75].

Because technology-based RCTs with cancer survivors remain infrequent, this study provides needed information regarding strategies that may improve efficacy. The site did not provide for direct participant interactions, which could improve engagement [76, 77]. Although the *INSPIRE* site was mobile enabled, it did not incorporate social media or texting which may improve the appeal to younger adults,[78] although other factors such as wanting to put cancer behind them or a focus on other aspects of life also contribute to their low participation rates in other studies [79]. As noted by Mohr and colleagues, to be effective, technology-based interventions must be integrated into the user's lifestyle and familiar manner of use of their devices [80, 81]. Therefore, particularly for younger adults, mobile applications and texting focused on shorter and more frequent interactions may be more effective [80]. Flexible methods that adapt to individual needs, including phone contact options, seem necessary to engage some survivors [82, 83]. While PST improved the efficacy of the intervention for distress, a relatively large proportion (22%) of those randomized to PST declined participation in calls. This suggests that a stepped care model adding telehealth calls only for those who do not improve with the online site alone may direct utilization of resources more efficiently [24]. Lack of intervention efficacy for fatigue and physical dysfunction highlights the need for a more interactive methodology to increase activity and reduce fatigue. The open-access online site may not be sufficiently powerful to alter exercise habits or alternatively the focus on physical activity may not be adequate to improve fatigue in these HCT survivors.

This study has several strengths and limitations. As strengths, we approached all survivors who were potentially eligible, and enrollment was high for an internet intervention. The sample size was large, whereas many online studies with cancer survivors are small pilot studies. The design was risk-based, focusing resources on survivors with the problems targeted by the intervention. Limitations included the requirement for internet access, a low rate of eligible minority survivors to approach and among enrollees, and enrollment was conducted at a single center. A multi-center trial may highlight different needs among a more sociodemographically diverse group of survivors.

In conclusion, this research demonstrates the promise of online and telehealth modalities for benefiting some HCT survivors, particularly for mood-based interventions. More work is needed to realize the full potential of technology-enhanced interventions, by optimizing delivery to those with needs and engaging diverse survivors, as well as defining effective intervention models for health needs other than mood. Technology-facilitated care has the potential to reach many more survivors than in-person interventions. Adding more tailored content and increasing interactive options, along with strategies for directing, tracking and motivating healthy behaviors may extend and improve the efficacy of online interventions.

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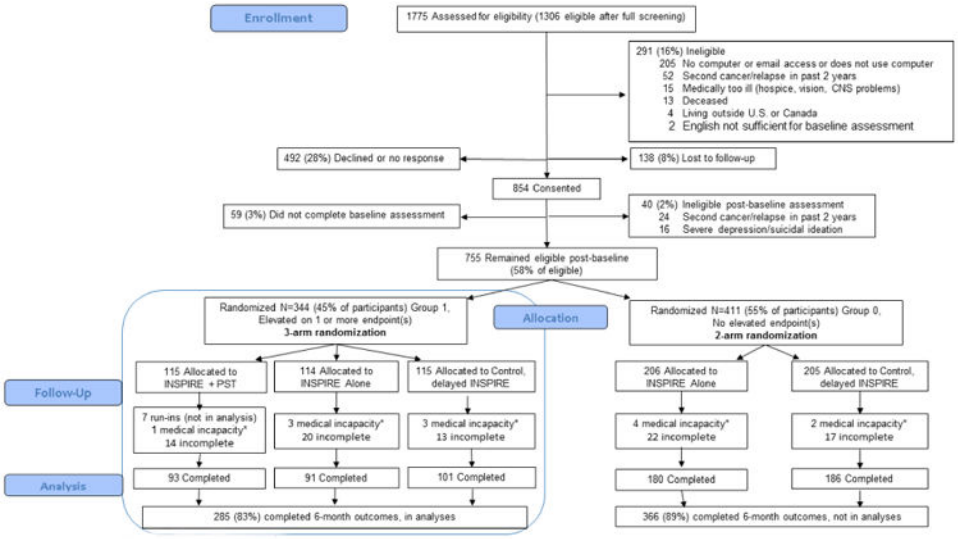

Figure 1. Consort diagram for study flow

* Relapse, hospice care, hospitalized so unable to respond

Table 1

Demographic and medical characteristics of eligible survivors not randomized and randomized

Variables and Categories:	Eligible survivors not randomized (N=551)	All randomized survivors (Groups 0 & 1) (N=748)	Group 0 randomized survivors, no elevated endpoints at baseline (N=411)	Group 1 randomized survivors, with one or more elevated endpoints at baseline (N=337)[a]	P value Not randomized vs. All randomized[b]
Age, Mean (SD)	51 (14)	52 (12)	52 (13)	51 (12)	
Range	18-79	18-78	18-78	18-76	
Categories, *n* (%)					**.001**
18-39	134 (24)	125 (17)	66 (16)	59 (18)	
40 or older	417 (76)	623 (83)	345 (84)	278 (82)	
Male, *n* (%)	326 (59)	416 (56)	239 (58)	177 (53)	.20
Rural, [c] *n* (%)	116 (21)	150 (20)	84 (20)	66 (20)	.66
Race, *n* (%)					**<.001**
African American	9 (2)	5 (0.7)	4 (1)	1 (0.3)	
Asian	29 (5)	16 (2)	7 (1.8)	9 (2.7)	
Native American/Alaska Native	8 (2)	2 (0.3)	1 (0.2)	1 (0.3)	
White/Caucasian	478 (87)	695 (93)	379 (92)	316 (94)	
Other non-white or mixed	10 (2)	30 (4)	20 (5)	10 (3)	
Unknown	17 (3)				
Ethnicity: Hispanic or Latino, *n* (%)	17 (3)	21 (3)	12 (3)	9 (3)	<.74
Unknown	25 (5)				
Diagnosis, *n* (%)					**.002**
Acute leukemia	149 (27)	225 (30)	122 (30)	103 (31)	
Chronic myelogenous leukemia	198 (36)	218 (29)	124 (30)	94 (28)	
Non-Hodgkin lymphoma	85 (16)	124 (17)	64 (16)	60 (18)	
Myelodysplasias	32 (6)	83 (11)	52 (13)	31 (10)	
Multiple Myeloma	41 (7)	58 (8)	30 (7)	28 (8)	
Hodgkin lymphoma	33 (6)	26 (3)	11 (3)	15 (4)	

Variables and Categories:	Eligible survivors not randomized (N=551)	All randomized survivors (Groups 0 & 1) (N=748)	Group 0 randomized survivors, no elevated endpoints at baseline (N=411)	Group 1 randomized survivors, with one or more elevated endpoints at baseline (N=337)[a]	P value Not randomized vs. All randomized[b]
Other	13 (2)	14 (2)	8 (1)	6 (1)	
Donor Type, *n* (%)					.66
Autologous	140 (25)	182 (24)	91 (22)	91 (27)	
Allogeneic	411 (75)	566 (76)	320 (78)	246 (73)	
Years post-transplant, *n* (%)					**<.001**
<10 years	287 (52)	477 (64)	249 (61)	228 (68)	
10+ years	264 (48)	271 (36)	162 (39)	109 (32)	
History of clinical chronic GVHD,[d] *n* (%)	243 (59)	421 (74)	227 (71)	194 (79)	**.03**

[a] Endpoints include distress, depression, or fatigue

[b] *P* value for chi-square test comparing all Group 0 and 1 participants to eligible but not randomized participants

[c] Urban/rural coding based on zip code tables from the Department of Social and Health Services, Center for Medicare Services[84]

[d] GVHD, graft versus host disease, reported only for those receiving allogeneic transplants

Table 2

Characteristics of participants with one or more elevated endpoints at baseline

Variables and Categories:	All Group 1 (N=337)	Group 1 *INSPIRE*+ PST[a] calls (N=108)	Group 1 *INSPIRE* Alone (N=114)	Group 1 Controls (N=115)	P value *INSPIRE +PST vs. Control*	P value *INSPIRE Alone vs. Control*
Age, Mean (SD) range	51 (12)	51 (12)	50 (13)	51 (11)		
Range	18-76	19-76	19-76	21-76		
Categories, *n* (%)						
18-39	59 (18)	17 (16)	21 (18)	21 (18)	.62	.98
40 or older	278 (82)	91 (84)	93 (82)	94 (82)		
Male, *n* (%)	177 (53)	58(54)	59 (52)	60 (52)	.82	.95
Rural,[b] *n* (%)	66 (20)	19 (18)	27 (24)	20 (17)	.97	.24
Race, *n* (%)					.63	.73
African American	1 (0.3)	1 (0.9)	0 (0)	0 (0)		
Asian	9 (2.7)	2 (1.9)	3 (2.6)	4 (3.5)		
Native American/Alaska Native	1 (0.3)	0 (0)	1 (0.9)	0 (0)		
White/Caucasian	316 (94)	102 (94)	107 (94)	107 (93)		
Other non-white or mixed	10 (3)	3 (2.8)	3 (2.6)	4 (3.5)		
Ethnicity: Hispanic or Latino, *n* (%)	9 (2.7)	3 (2.)	3 (2.6)	3 (2.6)	.94	.99
Education, *n* (%)					.71	.09
High School or less	26 (8)	9 (8)	6 (5)	11 (10)		
2 year college or more	281 (83)	90 (83)	98 (86)	93 (81)		
Unknown	30 (9)	9 (8)	10 (9)	1 (10)		
Income, *n* (%)					.79	.09
Below $40,000 per year	58 (17)	21 (19)	21 (18)	16 (14)		
$40,000-$79,999 per year	96 (28)	30 (28)	29 (25)	37 (32)		
$80,000 and above per year	142 (42)	45 (42)	49 (43)	48 (42)		
Unknown	41 (12)	12 (11)	15 (13)	14 (12)		

Variables and Categories:	All Group 1 (N=337)	Group 1 *INSPIRE*+ PST[a] calls (N=108)	Group 1 *INSPIRE* Alone (N=114)	Group 1 Controls (N=115)	P value *INSPIRE +PST vs. Control*	P value *INSPIRE Alone vs. Control*
Marital status, *n* (%)					.94	.12
Married or living with a partner	231 (69)	74 (69)	73 (64)	84 (73)		
Single, separated, divorced or widowed	80 (24) 26 (8)	26 (24) 8 (7)	33 (29) 8 (7)	21 (18) 10 (9)		
Unknown						
Computer Experience, *n* (%)					.84	.70
Beginner	53 (16)	17 (16)	19 (17)	17 (15)		
Intermediate/Expert	284 (84)	91 (84)	95 (83)	98 (85)		
Diagnosis, *n* (%)					.95	.59
Acute leukemia	103 (31)	35 (32)	37 (32)	31 (27)		
Chronic myelogenous leukemia	94 (28)	26 (24)	35 (31)	33 (29)		
Non-Hodgkin lymphoma	60 (18)	19 (18)	17 (15)	24 (21)		
Myelodysplasias	31 (10)	12 (10)	8 (9)	11 (10)		
Multiple Myeloma	28 (8)	11 (10)	7 (6)	10 (9)		
Hodgkin lymphoma	15 (4)	4 (4)	6 (5)	5 (4)		
Other	6 (1)	1 (2)	4 (2)	1 (1)		
Donor Type, *n* (%)					.46	.47
Autologous	91 (27)	32 (30)	28 (25)	31 (27)		
Allogeneic	246 (73)	76 (70)	86 (75)	84 (73)		
Years post-transplant, *n* (%)					.48	.93
<10 years	228 (68)	76 (70)	76 (67)	76 (66)		
10+ years	109 (32)	32 (30)	38 (33)	39 (34)		
History of clinical chronic GVHD,[c] *n* (%)	194 (79)	56 (74)	68 (79)	70 (83)	.18	.95
Current chronic GVHD,[c] *n* (%)					**.02**	.42
None	133 (54)	36 (47)	42 (49)	55 (66)		
Mild	74 (30)	26 (34)	30 (35)	18 (21)		
Moderate	33 (13)	9 (12)	13 (15)	11 (13)		

Variables and Categories:	All Group 1 (N=337)	Group 1 *INSPIRE*+ PST[a] calls (N=108)	Group 1 *INSPIRE* Alone (N=114)	Group 1 Controls (N=115)	P value *INSPIRE +PST vs. Control*	P value *INSPIRE Alone vs. Control*
Severe	6 (2)	5 (7)	1 (1)	0 (0)		
Cancer and Treatment Distress, *n* (%) >1.10	120 (36)	39 (36)	46 (40)	39 (34)	.36	.12
Baseline mean (SD)	0.99 (0.53)	0.97 (0.55)	1.06 (0.50)	0.94 (0.53)		
6 month mean (SD)	0.90 (0.54)	0.86 (0.56)	0.94 (0.51)	0.91 (0.55)		
Symptom Checklist 90-R Depression, *n (%) >1.0*	134 (40)	45 (42)	47 (41)	42 (37)	.43	.47
Baseline mean (SD)	0.94 (0.52)	0.96 (0.57)	0.98 (0.51)	0.88 (0.49)		
6 month mean (SD)	0.89 (0.56)	0.88 (0.62)	0.91 (0.51)	0.88 (0.55)		
Fatigue Symptom Inventory, *n* (%) *>4.7*	106 (31)	34 (31)	39 (34)	33 (29)	.65	.37
Baseline mean (SD)	3.68 (1.87)	3.73 (1.79)	3.75 (1.99)	3.57 (1.83)		
6 month mean (SD)	3.50 (1.90)	3.50 (1.88)	3.74 (1.94)	3.30 (1.87)		
SF-36 Physical Function, *n* (%) *T score <40*	104 (31)	38 (35)	31 (27)	35 (30)	.45	.59
Baseline mean (SD)	44.04 (10.73)	43.57 (11.00)	44.70 (10.74)	43.84 (10.51)		
6 month mean (SD)	44.69 (10.52)	43.76 (11.36)	44.83 (10.19)	45.41 (10.03)		
INSPIRE site number of pages viewed, *n* (%)						.67
0-1 page	73 (32)	33 (31)	38 (33)	NA[d]		
2+ pages	151 (68)	75 (69)	76 (67)	NA		

[a] PST, Problem Solving Treatment, seven participants randomized to the PST group were treated as practice run-ins and were not included in analyses

[b] Urban/rural coding based on zip code tables from the Department of Social and Health Services, Center for Medicare Services[84]

[c] GVHD, graft versus host disease, reported only for those receiving allogeneic transplants

[d] NA, not applicable

Table 3

Relative risks (RR) comparing rates of improvement in the 3 study arms for the primary outcomes at 6 months among group 1 participants impaired on that outcome at baseline assessment

Outcome measure and cut point indicating improved score	*INSPIRE* +PST[a]		*INSPIRE*		Control
	n/N (%)[b]	RR (95% CI)[c]	n/N (%)	RR (95% CI)[d]	n/N %
Cancer and Treatment Distress <1.11	15/33 (45)	**2.3 (1.0, 5.1)**	16/40 (40)	2.0 (0.9, 4.5)	6/30 (20)
Symptom Checklist 90-R Depression <1.0	12/38 (32)	0.9 (0.5, 1.7)	20/39 (51)	1.4 (0.9, 2.4)	14/39 (36)
Fatigue Symptom Inventory <4.7	14/31 (45)	0.9 (0.8, 1.0)	12/33 (36)	0.6 (0.4, 1.1)	17/30 (57)
SF-36 Physical Function >40	8/33 (24)	0.9 (0.4, 1.9)	9/36 (25)	0.9 (0.4, 1.9)	12/43 (28)

[a] PST, problem-solving treatment

[b] n = number improved on outcome at 6 months of those impaired on the outcome at baseline (N), % = percent improved

[c] *INSPIRE*+PST vs. Control: Distress: ***P* = 0.032**, Depression: *P* = 0.69, Fatigue: *P* =0.37, PF: *P* = 0.72

[d] *INSPIRE* Alone vs. Control: Distress: *P* = 0.075, Depression: *P* = 0.17, Fatigue: *P* =0.11, PF: *P* = 0.77