SCIENTIFIC REVIEW COMMITTEE

Title: Post-Chemotherapy Symptom Management: Testing Intervention Sequences in a SMART Design NCT03494166

KEY PERSONNEL

Name	Organization	Role on Project
Terry Badger, PhD	University of Arizona	Principal Investigator
Alla Sikorskii, PhD	Michigan State University	Principal Investigator
Chris Segrin, PhD	University of Arizona	Co-Investigator
Tracy Crane, PhD	University of Arizona	C-Investigator
Pavani Chalasani, MD, MPH	University of Arizona	Co-Investigator
Charles Given, PhD	Michigan State University	Consultant

SCHEMA OR FLOWCHART

Insert schematic or diagram outlining study design and procedures

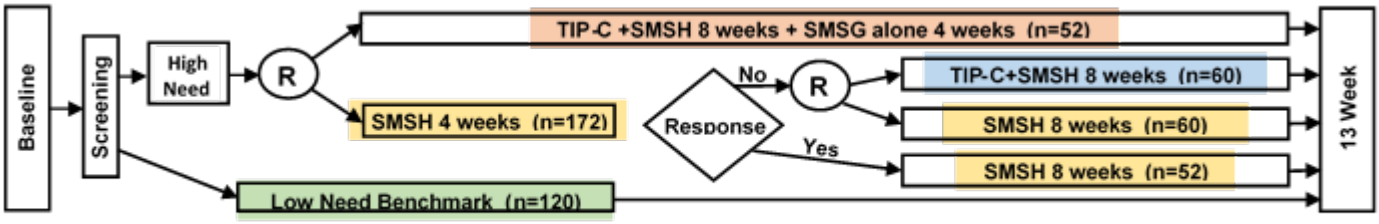


Figure 1: Intervention Scheme: R=randomization. Response evaluation after week 4.

1.0 BACKGROUND & RATIONALE

Scientific background and basis for hypothesis(es) to be tested. Include justification for conducting study and results of similar studies or pilot data.

Nearly 15.5 million Americans have survived cancer and virtually all have experienced symptoms from cancer treatment that negatively impact their quality of life.[1] Although numerous symptom management interventions have been tested during active cancer treatment,[2-5] few have addressed the continuing fatigue, pain, depression, anxiety, insomnia, and other symptoms that endure following the end of treatment.[6-10] Existing post-treatment symptom management research has targeted survivors several months after the end of active treatment, overlooking the immediate post-treatment period. During this period, some survivors have their symptoms resolve naturally with low need for interventions, while others suffer from high symptom burden, with about 30% experiencing depression.[11-13] Even when depressive symptoms are not sufficiently severe to warrant a clinical diagnosis of depression,[14-17] they need attention to decrease morbidity and mortality.[18-20]

Based on the work of this team [21-23] and others,[24-27] the number, severity and persistence of symptoms following chemotherapy for solid tumors can be predicted in part by comorbid conditions and depressive symptoms. Both of these easily identifiable factors influence the time needed to recover from cancer treatment,[28-30] and are associated with multiple symptoms.[31-36] Thus, we propose to target survivors with one or more comorbid conditions and elevated depressive symptomatology who are at risk for lingering symptoms that require interventions following at the end of chemotherapy; we call these "high need" survivors in this application. In our previous studies, 65% of survivors of solid tumors met these criteria and had higher persistent symptom burden than did survivors without these co-morbidities.[21-23,37]

Our scientific premise is that depression, prevalent at the end of chemotherapy, is an important cognitive and emotional barrier for self-management of symptoms. Building on this premise, we seek to determine if addressing depressive symptoms will allow survivors to reframe their beliefs regarding the efficacy of their actions towards managing their symptoms. The goal of this research is to determine the best sequencing of interventions for high need survivors using a **s**equential **m**ultiple **a**ssignment **r**andomized **t**rial (SMART) design (Figure 1). Two interventions with proven efficacy [4,37-39] will be used: 1) a minimal intervention, the printed Symptom Management and Survivorship Handbook (SMSH) with evidence-based self-care strategies for elevated symptoms and 2) a more intensive intervention that combines SMSH with a Telephone Interpersonal Counseling (TIP-C) intervention for managing depressive symptoms.[39,40] We follow the clinical logic of starting with SMSH, assessing its success in managing depressive symptoms (response), and continuing it when effective. If SMSH proves inadequate after 4 weeks for a survivor, we will test adding a more intensive TIP-C.

2.0 OBJECTIVE(S)/SPECIFIC AIMS

Purpose and specific aims of the study.

The proposed SMART will enroll an ethnically diverse (about 30% Hispanic) sample of N=344 (post-attrition) survivors of solid tumors at the end of chemotherapy. As in past work,[41-43] we will deliver the interventions in either English or Spanish, based on the participant's preference. The **specific aims** are to:

Aim 1. Test the effects of interventions on the summed index of severity of 15 post-chemotherapy symptoms (primary outcome) and symptom-specific responses and times to response (secondary outcomes).
Hypothesis 1. Survivors in the group that starts with TIP-C+SMSH versus to the group that starts with SMSH alone created by the first randomization will have better primary and secondary outcomes at weeks 1-13.
Hypothesis 2. Among non-responders to the SMSH alone after 4 weeks, survivors in TIP-C+SMSH as compared to the SMSH alone group created by the second randomization will have better primary and secondary outcomes at weeks 5-13.
Hypothesis 3. Self-efficacy and social support will mediate improvements in the primary outcome at week 13.
Aim 2. Compare symptom outcomes of intervention sequences against the benchmark low need group.
Exploratory Aim. Explore which survivor characteristics are associated with responses to the SMSH alone during weeks 1-4 and optimal symptom outcomes during weeks 1-13. This will allow us to determine tailoring variables to inform decision rules for choosing intervention sequences for individual survivors in the future.

The SMART design provides a state-of-the-art framework for rigorous testing of this innovative symptom management approach in the overlooked immediate post-chemotherapy period.

3.0 SAMPLE ELIGIBILITY CRITERIA

Specific inclusion/exclusion requirements which must be met for entry.

Inclusion criteria include: (1)18 years of age or older, 2) have access to a telephone, 3) understand English or Spanish, and 4) are not currently receiving counseling and/or psychotherapy. Survivors must: 5) have a new diagnosis or localized recurrence of solid tumor cancer, and 6) be finishing curative intent adjuvant chemotherapy or chemoradiation, and do not have any subsequent cancer treatments planned, except for radiation therapy, hormonal therapy or trastuzumab for breast cancer.

Exclusion criteria include: (1) diagnosis of a psychotic disorder in medical record verified by the recruiter; 2) nursing home resident; 3) bedridden; 4) currently receiving counseling and/or psychotherapy. For instance, the sample will include survivors finishing chemoradiation for stage III lung cancer, survivors of breast, colon, rectal, resected pancreatic or resected lung cancer.

4.0 PARTICIPANT RECRUITMENT/ENROLLMENT

Describe how study participants are to be recruited and enrolled in the study with appropriate contact phone numbers, etc. Stratification factors, participant characteristics which are balanced across treatment arms or used to determine intervention doses are described here. The randomization scheme is included here if applicable.

Recruitment and enrollment. The proposed SMART will enroll an ethnically diverse (about 30% Hispanic) sample of N=344 (post-attrition) survivors of solid tumors at the end of chemotherapy.

Survivors are recruited at the University of Arizona Cancer Center (UACC) locations in Tucson and Phoenix, Valleywise Health in Phoenix, and in the community. Recruiters (nurses or other health professionals) have research roles and do not provide direct care at the participating oncology settings. Survivors will be assured of the confidentiality of all information provided and that refusing to participate will not alter their health care. Survivors will continue to receive standard medical and nursing care, so they may seek care from their health providers for any health problems that arise. For

those who refuse, the recruiter will ask their reason for refusal. For those who agree to participate, the recruiter will obtain the consent form, confirm treatment plan, and complete the recruitment form that includes name, main and alternative contact information, convenient call time, cancer site and stage, names and contact information for oncologist and primary care physician. Study participants will be informed that they will be 1) randomization to SMSH or TIP-C+SMH and may be re-randomized after 4 weeks to either continue with the SMSH alone or to add TIP-C, 2) telephone symptom assessment and intervention sessions are weekly, and 3) there is no cost to study participation. Further, 4) the study lasts 13 weeks to include all data collection, 5) Interventions are designed to help reduce symptoms, 6) A review of potential risks/benefits; and 7) there are study incentives.

Using the inclusion/exclusion requirements detailed in section 3.0, the sample will include survivors finishing chemoradiation for stage III lung cancer, survivors of breast, colon, rectal, resected pancreatic or resected lung cancer. Because site of cancer and treatment type are balancing factors in randomizations, these variables will be equally distributed among trial arms. Our prior research indicates that participation in counseling and/or psychotherapy is rare. This exclusion criterion will not substantially limit the population but will eliminate potential confounding of the intervention effects with extraneous influences. Based on the demographic characteristics of the AZ population, the sample will consist of approximately 60% non-Hispanic white, 30% Hispanic/Latino, 3% each African American and Asian American, and 4% American Indian participants. There is an ample pool of cancer survivors available to meet enrollment targets. In 2017, Arizona is estimated to have 35,810 newly diagnosed cases of cancer,1 of these the majority are solid tumors. Conservatively, we will have access to about 10%, of which approximately 1/3rd or 1000 will satisfy the inclusion criteria. If 1/3rd of these, or 330, are approached and half will consent to participate, we can recruit over 160 survivors per year. Given this team's past successful recruitment at the UACC and community sites (see letters of support), the proposed study will easily meet the goal of 145 survivors per each of 3 years of recruitment.

Sample Size and power considerations. To determine sample size, we started at the right of the schematic in Figure 1 (the second randomization) and moved from right to left to determine the number of survivors needed. To power the comparisons of groups created by the second randomization (Hypothesis 2), we used the effect size of Cohen's d=0.39 (adjusted for baseline), the smallest seen in the preliminary data for TIP-C against an educational intervention (Table 2) to conservatively estimate sample size requirements. We further adjusted this effect size for the reduction in error variance due to 9 repeated measures of the primary outcome. In past studies, Pearson correlation coefficients between pairs of repeated measures of summed symptom severity index ranged from r=0.36 to 0.77, resulting in the range of the adjusted effect sizes from d=0.54 to 0.84. Using the smallest adjusted d=0.54, the required sample size is 60 per group created by the second randomization, for power of .80 or greater in two-tailed tests at the 0.05 level of significance. For the analysis of symptom response, the unit of analysis will be participant-symptom. Based on the preliminary data and inclusion criteria, 120 participants from the second randomization are expected to average 2.7 symptoms at moderate or severe levels, yielding 324 symptom cases treated as nested within participants as described in the analysis. After accounting for nesting of the symptom cases within survivors, the adjusted sample size for the analysis of symptom response is 248 symptom cases, or 124 per group. Examples of detectable differences include symptom response of 47% versus 30%, rates consistent with past studies.[139,152] Proceeding further from left to right in Figure 1, 120 dyads from two groups created by the second randomization will be non-responders on depression to the SMSG alone after 4 weeks. From past work, the response rate to the SMSG on depression was 30%,[97] therefore 120 non-responders will be 70% of 172 randomized to the SMSG alone in the first randomization. The comparison of 172 to 52 participants allocated to the TIP-C+SMSG in the first randomization will have power of 0.92 to detect the effect size of 0.54 (adjusted for the repeated measures) in testing the hypotheses associated with Hypothesis 1. The tests of mediation effects (Hypothesis 3) will have an even greater power than the comparisons of

randomized arms because of further reduction in error variance. Formal power considerations are not applicable for the exploratory aim. Therefore, the post-attrition size of the high need group is N=224. Since this group is 65% of the survivors finishing chemotherapy, we will screen 344, leaving 120 in the benchmark low need group. To account for 20% attrition based on past work, we will need to have 430 survivors' consent.

Subject incentives. Incentive payments not only significantly improve recruitment rates[165], but there are no significant differences in key dependent variables for those offered versus those not offered an incentive.[166] Provision of incentives equivalent to the demands of participation is vital to successfully recruiting minorities into research and getting a culturally representative diverse sample.[167-170] After every interview, participants will receive thank you letters and gift cards from a large retail merchant in graduated amounts ($40 after baseline and $50 after week 13). The total compensation will be $90 for about 6-7 hours of participants' time over 13 weeks in the high need group, or 2 hours in the low need group.

Strategies to minimize attrition. 1) Recruiters will emphasize the importance of participating in the entire study. 2) Survivors will be asked to mark their calendars for study calls. 3) E-mail or text reminders are sent about upcoming telephone contacts if agreed to by participants. 4) Weekly calls will maintain contact for the entire study duration. 5) Graduated compensation is provided for assessment sessions. These strategies have worked well in the past, with retention rates of ≥75%.

Community ties and cultural sensitivity. We use experienced staff members with extensive ties to the local survivorship communities. The study brochures will be developed in English and in Spanish with community advisors.[39,40] Seven principles of language competence, cultural competence, ethical conduct, mission or purpose, empathy, graciousness and credibility[171] will be incorporated in all interactions. We will show cultural sensitivity along two dimensions.[172,173] Surface structure involves matching messages to observable 'superficial' characteristics of the target population (e.g., speaking English or Spanish). Deep structures involve incorporating some of the socio-cultural, historical, environmental and psychological forces that influence health behaviors. For example, we will incorporate the value of *personalismo* by talking about participants' lives at the beginning of sessions. Participants from past studies have appreciated the flexibility and respect (*respeto*). [174] These techniques allow us to personalize our interactions, addressing both personal and cancer issues of concern. This approach is critical to gain trust (*confianza*).

Management of post-chemotherapy symptoms: high versus low need. Breast cancer has been the focus of the few intervention studies designed to support patients as they finish chemotherapy.[6,7,72,73] Post- treatment interventions produced modest benefits for fatigue,[6,7 72,74] other symptoms,[75,76] or overall quality of life.[61,77] The modest effects observed may be due, in part, to directing interventions toward those who may not need them along with those who do, creating a floor effect for symptom reductions and diluting the improvements realized among those in the high need subset. This application addresses these problems by separating out a group with low need for symptom management and intervening with only a predefined high need group in an ethnically diverse (at least 30% Hispanic) sample of survivors of solid tumors. Survivors will be stratified according to the need for management of post-chemotherapy symptoms with two identifiable factors (comorbid conditions and depressive symptoms). The first factor, comorbidity, negatively affects the health status prior to the cancer diagnosis.[78] During cancer treatment, chemotherapy exacerbates comorbidity- related impairments in health status.[79-84] Comorbid conditions as important predictors of treatment[85] and treatment outcomes,[79-84,86-94] may influence the time needed to recover from cancer treatment,[28,29] and are associated with multiple symptoms.[79,82] As for the second factor, there is strong evidence that

depressive symptoms influence severity of other symptoms, and extend recovery from treatment.[60,80,95] Although many survivors suffer from depressive symptoms that are not sufficiently severe to warrant a clinical diagnosis of depression,[14-17] these symptoms need attention and are highly treatable.[18,20]

Table 1: Prevalence of moderate or severe symptoms at 2 and 8 weeks post chemotherapy	High need group, N=87		Low need group, N=56	
	2 weeks, (%)	8 weeks (%)	2 weeks (%)	8 weeks (%)
Fatigue	39.08	39.08	26.79	23.21
Pain	27.59	22.99	8.93	5.36
Weakness	26.44	20.69	5.36	7.14
Distress	22.99	21.84	7.14	5.36
Dyspnea	21.84	19.54	10.71	8.93
Insomnia	20.69	20.69	25.00	12.50

Based on this body of literature, comorbidity and depressive symptoms will determine the need for postchemotherapy symptom management. The use of these factors for the need determination is further supported by our past work with survivors during chemotherapy, in which we followed a subset of N=143 into the postchemotherapy period (Table 1 for 5 most prevalent symptoms).[21,22] Survivors with at least one comorbid condition and a Center for Epidemiologic Studies- Depression (CES-D) score of ≥16 (the established clinical cut point)[96] at the end of chemotherapy (high need) had higher persisting symptom burden compared to patients with no comorbid conditions or CES-D score < 16 (low need). Moderate or severe fatigue, pain, weakness, distress, dyspnea, and insomnia, as defined by previously established validated cut-points,[97] persisted in over 20% of high need survivors for at least 8 weeks post-chemotherapy. Survivors in the high need group experienced on average 2.7 moderate or severe symptoms at 2 weeks post chemotherapy, and 2.3 at 8 weeks. In contrast, the prevalence of residual symptoms in the low need group was lower at week 2. If it was higher (e.g., insomnia), it declined without interventions at week 8. The mean number of symptoms in the low need group was 1.6 at week 2, and 1.1 at week 8 post-chemotherapy. Among survivors with one or more comorbid condition, those with CES-D scores ≥ 16 did not differ on severity of depression with respect to specific comorbidities. These findings are consistent with a review of 34 studies,[98] where the number but not specific combinations of comorbid conditions were related to the outcomes of chemotherapy. Thus, the strata we propose are robust and not influenced by specific comorbid conditions. The proposed work builds on this highly significant evidence to conserve resources by targeting only a group of survivors with high need for symptom management interventions.

The low need survivors will not receive interventions but will be followed up over time to confirm that they are experiencing a natural resolution of symptoms following the end of chemotherapy. Their symptom outcomes are benchmarked against those produced by the intervention sequences. For example, while symptom severity may be lowered by the intervention in the high need group, would severity be at the same level as in the benchmark group? Because the low need group is created using stratification and not randomizations, the conclusions from the comparison to high need patients will not be causal. Instead, this comparison will allow us to gauge the clinical significance of the results and their relevance to survivors

Hispanic/Latino Survivors. Given the increasing population of Hispanic cancer survivors, providing and testing an intervention in the participant's primary language could have national significance. In our past work with non-Hispanic samples, 65% were in the high need group,[21,22] and this percentage may be

larger among Hispanic survivors who have a higher prevalence of depression and comorbidity compared to non-Hispanic whites. [99,100] [101-104] In our studies with relatively young (median age 44 years, N=293) Hispanic women with breast cancer at varying points in survivorship, 35% had hypertension, 35% had heart disease; 15% had diabetes, and BMIs averaged 31.5, [range 19.7-54.1]. Prevalence of depression was 49% overall, and 59% among those who had received chemotherapy and radiation. While these women were not specifically assessed at the end of chemotherapy, depression is expected to be higher at the end of treatment.[61]

5.0 RESEARCH DESIGN, METHODS AND PROCEDURES

Describe research design, methods and all study procedures

Design. Using the SMART design (Figure 1), we will recruit 430 survivors finishing curative intent chemotherapy or chemo-radiation for a solid tumor at the NCI-designated University of Arizona Comprehensive Cancer Center (UACC, Tucson and Phoenix locations) and at Arizona (AZ) community oncology settings (post attrition N=344). Following consent, we will collect all further data and deliver interventions over the telephone from the central study office. The study Coordinator will conduct recruiter training. Training will include didactic information, role-playing, and return demonstration of recruiting per script. Study participants will be informed that they will be 1) randomization to SMSG or TIP-C+SMSG and may be re-randomized after 4 weeks to either continue with the SMSG alone or to add TIP-C, 2) telephone symptom assessment and intervention sessions are weekly, and 3) there is no cost to study participation. Further, 4) the study lasts 13 weeks to include all data collection, 5) Interventions are designed to help reduce symptoms, 6) A review of potential risks/benefits; and 7) there are study incentives.

Following baseline interview, symptom management need (high versus low need) will be determined. The low need group will not receive interventions but will be followed up at week 4 for a brief symptom assessment and at week 13 for the exit interview. The survivors in the high need group will be randomly assigned to either: 1) SMSH alone or 2) TIP-C+SMSH for 8 weeks followed by continued 4 weeks of SMSH alone. We will mail the SMSH, printed in the survivor's preferred language, to the survivor following randomization. All high need participants will receive weekly telephone contacts during weeks 1-12 to assess symptoms, deliver the assigned intervention, and assess intervention enactment and fidelity.

After the initial 4 weeks in the SMSH alone group, the survivor's response on depression will be determined (see Survivor's symptom response). Responders will continue with the SMSH only for another 8 weeks. Survivors who do not respond on depression will re-randomized to either continue with the SMSH alone or add TIP-C to test the value added by the more intensive intervention. Those initially randomized to TIP-C+SMSH will not be re-randomized. Total duration of each of the three intervention sequences is 12 weeks: SMSH alone; SMSH alone for 4 weeks followed by SMSH+TIP-C for 8 weeks; TIP-C+SMSH for 8 weeks followed by SMSH alone for 4 weeks. The 8-week duration of TIP-C establishing the intervention dose is based on our past work. Week 4 timing for response determination is founded on past work:[137-139] where it was a change-point in the trajectory of the mean symptom severity, with median time to response on depression ranging from 14 to 24 days depending on patient and disease characteristics. Survivors in the low need benchmark group will also be assessed at week 4 to track the natural resolution of symptoms. The interview at week 13 will occur for both the survivors in the high need group after completing the 12-week intervention and for the low need benchmark group to achieve comparability for time. Our preliminary data indicate that at 12 weeks post chemotherapy, the prevalence of symptoms is low in the benchmark group, and the interventions have the potential to manage symptoms for high need survivors. Week 13 will conclude the data collection and follow-up.

We will extract cancer and treatment information from the oncology medical records after survivors complete the study.

Procedures.

Determination of need for symptom management. High versus low need status of survivors will be determined using data from the baseline telephone interview conducted within after consent. The criteria for being in the high need group are at least one comorbid condition as reported by patients using the Bayliss instrument[175] plus a CES-D[96] score of 16 or higher or two or more comorbid conditions (not including cancer) regardless of CES-D score. Survivors not meeting these criteria will be assigned to the low need benchmark group and sent a letter indicating that they will be contacted at 4 and 13 weeks for follow-up assessments.

High need group: randomizations. All high need survivors will be mailed a copy of the printed SMSH. In the first randomization, 52 survivors will be randomized to TIP-C+SMSH, and 172 survivors will be randomized to SMSH alone to ensure a sufficient number to investigate intervention sequencing (see power analysis). Randomization will be completed using a computer minimization algorithm[176,177] programmed by Dr. Sikorskii that balances arms by recruitment location (UACC versus community clinics), site of cancer, and type of cancer treatment received (chemotherapy, chemoradiation, chemotherapy followed by radiation therapy, hormonal therapy or trastuzumab).[176] The minimization is superior to stratified randomization and is well-suited for the design, as the groups are balanced dynamically with respect to selected variables, with each subsequent randomization targeting any imbalances between the groups that may have occurred previously. The second randomization will have a 1:1 ratio but the same balancing factors. It will occur after 4 weeks among non-responders to SMSG alone on depression, a sentinel symptom that is associated with other symptoms[68-71] and a barrier to their self-management,[37,114,115] based on our scientific premise.

Survivor's symptom response. Response to the management of each of 15 symptoms will be assessed using the symptom severity ratings from the General Symptom Distress Scale (GSDS) administered during weekly calls and interference-based cut-points for moderate or severe symptoms developed and validated in past work of this team.[97] Our approach overcomes the drawbacks of other approaches that are based on absolute or percent change[178,179] in severity, and anchors symptom responses to significant reductions in symptom interference with enjoyment of life, relationships with others, general daily activities, and emotions. As the symptom severity rating increases from 0 (not present) to 10 (worst possible), symptom interference increases as well, but does so in a non-linear way. The increase of one unit on the severity rating scale may have a different meaning in terms of symptom interference depending on where on the scale the increase occurs. The cut-points for mild, moderate, or severe symptom categories mark the places on a 0-10 scale where the largest increases in interference occur. The cut-points vary for different symptoms, reflecting their different degree of interference with daily life. For depression, the none/mild category corresponds to severity scores of 0-1, moderate category corresponds to scores 2-3, and scores of 4-10 are the severe category. For pain and fatigue, the none/mild category corresponds to severity scores of 0-1, the moderate category corresponds to scores 2-4, and scores of 5-10 fall into the severe category. For insomnia and numbness, the none/mild category is 0-3, moderate is 4-6, and severe is 7-10. We define onset for each symptom as the date when a symptom first reached moderate or severe according to these cut-points. Survivors who started at severe at onset and ended at moderate or mild at a given time point (e.g., week 4), and survivors who started at moderate and ended at mild, will be called responders for the specific symptom.[97] Thus a survivor may be, for example, a responder on pain and depression, and non-responder on fatigue. Symptom cases that remain or become moderate or become severe at

week 4 are classified as non-responders. We have selected response on the symptom of depression as a criterion for re-randomization at week 4 based on our scientific premise.

Interventions. This project will test two interventions: a Symptom Management and Survivorship Handbook (SMSH), and a Telephone Interpersonal Counseling (TIP-C). The SMSH is an evidence-based self-care management guide. The printed SMSG has specific symptom modules written at the 8th grade level.[84] Management strategies for each symptom are based on the National Comprehensive Cancer Network (NCCN) guidelines and the Oncology Nursing Society Putting Evidence into Practice (PEP) guides.[83,88] Modules on survivorship are based on the American Society of Clinical Oncology (ASCO) Guidelines for breast and colorectal cancer survivors.[105,106] A research assistant assesses symptoms and refers survivors to the specific SMSG sections for elevated symptoms during weekly phone calls. In past studies, survivors were satisfied with this intervention and reported decreased symptom burden and improved psychosocial status.[107]

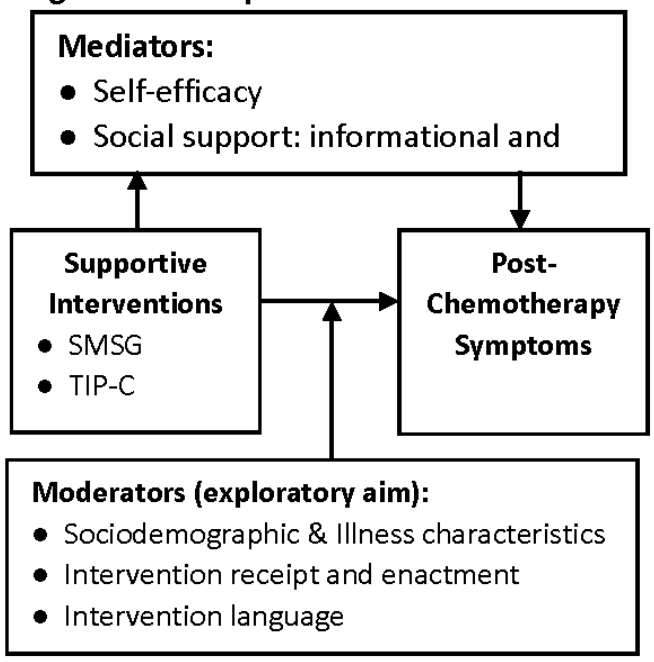
The Telephone Interpersonal Counseling (TIP-C) Intervention, based on interpersonal psychotherapy, has been shown to decrease psychological symptoms in past studies.[108-111] Social workers (called counselors) with a master's degree and psychiatric-mental health and oncology expertise deliver the TIP-C intervention via weekly calls. Counselors use interpersonal communications techniques to focus on depression, anxiety, and the interpersonal interactions between the cancer survivor and others. The counseling addresses 1) mood and affect management, 2) emotional expression, 3) interpersonal communication and relationships, 4) social support, and 5) follow-up, resources and referral to resources (e.g., financial). Negative psychological symptoms were shown to decrease with TIP-C in past studies [108-112] Other symptoms decreased with TIP-C,[113] which is consistent with the literature documenting the co-occurrence of depression with other cancer- and treatment-related symptoms [68-71] and that when depression is treated, other symptoms improve.

We will deliver interventions by telephone at convenient times for the survivor, including evenings and weekends, in English or Spanish, based on the survivor's preference. Section 7.0 details the intervention procedures for this study.

Methods

Dynamic intervention sequencing. By individualizing intervention sequences, this research overcomes a static approach to intervention delivery[116-118] by stepping up intervention intensity based on the survivor's demonstrated needs. We have established the efficacy of both TIP-C and SMSH (see section titled *preliminary studies*) in traditional RCTs. In the proposed study, we will investigate their optimal sequencing to address heterogeneity of response using a SMART design.[119-122] Our approach begins with one intervention, and then at a decision point typical in clinical practice, we will evaluate therapeutic response (as detailed in section on Survivor's Symptom Response). The analysis of data from this SMART will provide an evidence base for a decision to either give one intervention more time for symptom resolution or intensify by adding a second therapeutic modality. Currently, such decisions have a limited evidence base using individuals' characteristics. We will address this gap in science by building algorithms for allocating intervention resources in a way that leads to the best possible survivor outcomes using the most labor-efficient intervention to achieve those outcomes.

Figure 2: Conceptual Model of Intervention Effects



Conceptual framework. This study is informed by the NIH Symptom Science Model.[123] In our adaptation (Figure 2), depressive and other symptoms (e.g., fatigue, insomnia, pain) experienced by the survivor following chemotherapy are managed using the SMSG and TIP-C interventions[124] through key mediating variables, self-efficacy and social support, as tested in Hypothesis 3. By the design of these interventions, symptom improvement occurs in part by increasing self-efficacy to perform tasks (e.g. symptom management) [125-128] and mobilizing social support.[129] The mediated relationship of the intervention on symptoms may be influenced by "context of care" variables[130] that include socio-demographic, disease and treatment characteristics, the extent of intervention receipt and enactment,[131] and language of delivery that reflects the participant's preference and culture. These variables are considered as potential moderators in the exploratory aim of this study. Due to randomizations, these variables will be equally distributed among groups and will not affect the estimates of main intervention effects in Hypotheses 1-3. However, given these variables, intervention effects may differ for individuals, and these variables provide a pool of potential tailoring factors for the decision rules for choosing optimal intervention sequences (exploratory aim). For example, the analysis may determine that younger survivors do best with a simple SMSH for 12 weeks, while older survivors need TIP-C+SMSH at the end of chemotherapy to achieve optimal outcomes. Other context of care variables may warrant SMSH alone for 4 weeks with possible later step-up based on 4 weeks of data.

Preliminary Studies.

Evidence of the efficacy of the TIP-C intervention. Drs. Badger and Segrin, developers of the TIP-C, have tested it against attention control (AC), telephone health education (THE) or exercise.[43,140,141] Survivors were recruited together with their friend or family caregivers and randomly assigned to either TIP-C or a comparison group in each study and completed at least three assessments over time. TIP-C focuses on the psychological distress of the survivors and their interpersonal interactions with others. During 30-minute weekly sessions, counselors address 1) mood and affect management, 2) emotional expression, 3) interpersonal communication and relationships, 4) social support, and 5) follow-up and referral to resources (e.g., insurance, financial). Findings from our initial study141 showed survivors' depressive symptoms decreased over time for dyads in all groups (TIP-C, AC, exercise), and anxiety decreased in the TIPC and exercise groups. Based on initial testing and results of a meta-analysis, the TIP-C protocol was extended from 6 to 8 weekly sessions because those who were most depressed did better with more sessions/time.142 In the next two studies[42,43,113] and in our ongoing study with Latina dyads (current N=238 dyads, final N=250 dyads) which will be completed by December 2017,[143] we found significant decreases over time in depression, anxiety, negative affect, symptom distress and higher social support for survivors and caregivers, with TIP-C superior to THE on outcomes listed in Table 2. These preliminary data provide evidence for the efficacy of the TIP-C for managing depressive symptoms.

Table 2: Post-intervention least square (LS) means, standard errors (SE) and effects sizes (Cohen's d) for the TIP-C v. THE			
Outcome	TIP-C, LS Mean (SE)	THE, LS Mean (SE)	d
Symptom distress	5.12 (0.31)	5.87 (0.48)	0.44
Mental fatigue	5.41 (0.67)	6.91 (0.96)	0.39
Social well-being	67.00 (1.74)	56.12 (3.18)	1.04

Evidence for the efficacy of the SMSH. Drs. B. and C. Given, developers of the SMSH, have tested it in 4 RCTs with Dr. Sikorskii. Automated telephone symptom management using the SMSH was not different from nurse-assisted symptom management (N=437),[138] previously found efficacious against control.[144] Both arms achieved clinically significant reductions in symptom severity over baseline. In a recent study with 272 survivors treated with oral oncolytic agents,[145] significant declines in symptom severity in the SMSH+ oral agent reminders arm compared to attention control were found post intervention (p=.02). These studies provide evidence of the efficacy of SMSG for managing multiple treatment-related symptoms.

Telephone delivery of the interventions and data collection. In our initial studies, we used the telephone to deliver the interventions to remove access barriers to intervention receipt. Barriers are geographic access (e.g., rural), transportation costs, stigma, and the technology-associated anxiety and costs associated with internet delivery methods. Nationally, most people (98%) have telephone access146 whereas internet and computer access is less universal. Adherence to a telephone intervention in our past studies was approximately 85% which is double that for face-to-face counseling.147 In our past work, we found intervention delivery via face-to-face, videophones, internet, and interactive voice response systems inferior to a live person on the telephone with respect to adherence and participant satisfaction. Consistent with findings of others148, we found that telephone collection reduces missing data (<5%). For our participants with lower education and literacy, data collection is better when they can ask questions immediately. Finally, by using uniform telephone assessments in all arms, the effects of the mode of administration of symptom assessments will be avoided.149 After careful consideration, we will use the telephone for intervention delivery and data collection to facilitate success and scientific rigor of this project.

Delivery of the intervention in either English or Spanish. We have successfully delivered the TIP-C intervention in Spanish from bilingual bicultural counselors in a way that is culturally competent. We have incorporated Latina/o cultural values (see C5e) and beliefs about the importance of immediate and extended family and close friends in health outcomes.[15]

Training and intervention fidelity. Intervention fidelity will be assessed through established methods outlined by the NIH Treatment Fidelity Workgroup on consistency in dose, providers, delivery, and receipt of the intervention.[183] TIP-C interventionists (called counselors) will receive 24 hours of education, augmented by additional books and articles, about cancer diagnosis and treatment, psychological distress, and interpersonal counseling techniques with training protocols developed in previous studies.[150,154,184,185] The interventionist will listen to 8-10 hours of counseling sessions recorded for training purposes. Drs. Badger and Segrin will conduct intervener training that will continue until the interveners are rated as achieving > 90% on protocol implementation. Annual re-training will occur throughout the study**.** The intervention fidelity protocols used in past studies will be applied in this study. All sessions are digitally recorded and about 10% randomly reviewed throughout the study to maintain quality, with written and verbal feedback to the counselors. Drs. Badger and Segrin will supervise the intervention quality control activities. Through weekly supervision, we will maintain

intervention fidelity and counselor adherence to protocols. We will evaluate adherence (number required elements discussed/ total number of elements).[113,151,186] Drs. Badger and Segrin will listen to all sessions in English from the first 5 survivors (10 hours of supervision) and then randomly review 10% of sessions throughout the study. A bilingual counselor will review Spanish sessions using established protocols as in past studies. Counselors who do not maintain 90% adherence will not receive new cases until retraining has occurred, and Drs. Badger or Segrin will assume responsibility for those existing cases. Following retraining, 5 survivors will be monitored to insure that >90% adherence is achieved and then we will return to randomly selected monitoring for quality control. After a second retraining, we will replace counselors if unable to adhere to the protocols. Counselors deliver only the intervention for which they have training: 1) one for TIP-C +SMSH and 2) a different interventionist for SMSG alone. SMSG alone training will take less than two hours based on previous work by Dr. Sikorskii.

Intervention reproducibility. Interventions are standardized, yet the complexities of depressive symptoms demand a flexible approach to preserve the relevance of TIP-C for the survivor. We will determine the number of elements personalized to the specific needs within the structured protocol (number of personalized elements/ total number of elements). We will then examine the effect of personalization (e.g., more discussion of socioeconomic needs with one participant vs. another), if any, on outcomes. Counselors will keep detailed field notes after each session assessing intervention length, rapport, responsiveness, topics discussed, homework completed and satisfaction. Our past adherence rate of >85% far exceeds the rate reported for community mental health patients who return for face-to-face appointments.[187] Participants who miss (occurrence is rare) reschedule the session and as we will obtain multiple points of contact (e.g., home, cell, work telephone, e-mail address). If we fail to contact within the week, we will schedule the following week. We will document attrition rates and reasons.

6.0 MEASURES/DATA COLLECTION INSTRUMENTS

Describe all forms, questionnaires, instruments or other specific methods used to collect data. Include complete copies of all forms, interview guides, survey questionnaires, in Appendix I.

Data Collection

Interviews. All survivors will have data collected twice via telephone interviews: baseline and study week 13. The interviews will take 30-45 minutes. If a participant becomes fatigued, we will divide the telephone interview into two phone calls within the same week. Few participants requested such accommodations in past studies. Respondent burden is minimum and distributed over the course of the study. The interviewers at baseline and week 13 will be blinded to survivor's need status or intervention sequences received. The study Coordinator will train interviewers via didactic information, written steps, and role-playing for difficult interview questions. In addition, 10% of all interviews are recorded for quality assurance (QA).

Weekly Calls. Weekly symptom assessments are part of the delivery of SMSH and TIP-C interventions for the high need group (see section 7). At week 4, the study Coordinator will make a symptom assessment call to the survivors in the low need group using the GDSD to assess their natural symptom resolution.

Medical Records. Recruiters will extract medical records information after survivors complete the study.

Measures

All measures have good reliability (α >.80)[38,150,185,188] and validity, have been translated, and tested with Spanish speaking participants in our pilot studies.[39, 180] Patient Reported Outcomes Measurement Information System (PROMIS)[189,190] measures have been developed using sophisticated measurement

techniques, tested with over 21,000 individuals, calibrated to produce t-scores based on the general population, and are available in either English or Spanish. Measures are in Appendix A.

Primary outcome

Symptoms will be measured using the adapted General Symptom Distress Scale (GSDS),[190,191] that allows for a quick assessment of symptoms, which is especially important during weekly calls. It evaluates 18 symptoms: fatigue, sleep difficulties, pain, headache, difficulty concentrating, lack of appetite, nausea, vomiting, constipation, diarrhea, numbness or tingling, skin rashes, swelling, weakness, shortness of breath, cough, depression, anxiety. Respondents indicate presence of each symptom (yes/no) and rate their severity if present on the scale from 1 to 10. The ability to manage symptoms is also assessed on a scale from 0=cannot manage to 10=can manage extremely well. The GSDS has good test-retest and internal consistency reliability (≥0.8) and predictive and construct validity in both English and Spanish.[191] A summed symptom severity index will be derived from each weekly contact, baseline, and 13-week interviews.

Secondary outcomes

We will consider responses that are specific to each of the multiple symptoms that will be treated as nested within survivors. Response on depression will be applied as the criterion for re-randomization at week 4. Responses for all 15 symptoms during weeks 1-13 will be defined for Hypothesis 1, and responses during weeks 5-13 will be defined for Hypothesis 2. For responders, time to response will be defined as time in days from symptom onset to the date of the first sustained improvement among none/mild, moderate or severe categories. For non-responders, time to response will be treated as censored according to the principles of survival analysis.

Depression. The Center for Epidemiologic Studies – Depression (CES-D) scale is a widely used measure of depressive symptoms within non-psychiatric populations.[92,192,193] This measure has a reliability exceeding .90. At baseline, it will be used for need status determination, and at week 13 it will provide an additional measure of depressive symptoms to supplement the GSGS depression item.

Comorbidity. Comorbidity will be measured with the Bayliss tool that queries the presence of 20 comorbidities[175] and used for need status determination at baseline. The internal consistency reliability is not applicable to a checklist.

Potential Mediators. PROMIS short forms (SF) have established validity and $\alpha > .80$. [189,190,194]

Self-efficacy. The PROMIS 8-item SF will be administered in interviews.[195-198] Self-efficacy symptom management will also be captured by the GSDS item described above during interviews and weekly calls.

Social support. The PROMIS 8-item SF for instrumental and emotional support will be used in interviews.[195-198]

7.0 DETAILED DESCRIPTION OF INTERVENTION

Describe in detail for intervention studies or indicate otherwise by checking below:

Two interventions with proven efficacy [4,37-39] will be used: 1) a minimal intervention, the printed Symptom Management and Survivorship Guide (SMSG) with evidence-based self-care strategies for elevated symptoms and 2) a more intensive intervention that combines SMSG with a Telephone Interpersonal Counseling (TIP-C) intervention for managing depressive symptoms.[39,40]

a). Symptom Management and Survivorship Handbook (SMSH) contains 15 symptom-specific modules for the symptoms assessed in this study. Each module has an identical format (Frequently Asked Questions): what the symptom is, how people describe the symptom, the causes of the symptom including medications, and a set of strategies presented in bullet points for managing the symptom. For each symptom, there are indications as to when and for what reasons to contact the health

care provider and other resources are listed for management. Modules on survivorship are based on the American Society of Clinical Oncology (ASCO) Guidelines for breast and colorectal cancer survivors.[105,106] The previously tested English version was translated into Spanish using an adaptation of Brislin's translation/back translation process180 used by this team in the past. Professor Jaime Fatás-Cabeza, Director of the Undergraduate Translation and Interpretation Program in the Department of Spanish and Portuguese at the University of Arizona, oversaw the translation of the SMSH, producing a Spanish language version suitable for readers with an 8th grade education. Three cultural experts performed back translations of a random sample of pages from the SMSH for comparison to the original English language versions, and all discrepancies between the back translated and original English language pages were corrected. The translated version was discussed in a focus group of six Spanish-speaking Latinos in terms of understandability (language level and complexity), use of idioms, and consistency of meaning.

All high need survivors will be mailed the SMSH in English or Spanish (participant preference), following the completion of the baseline interviews. During each week, the research assistant (RA) trained by the study Coordinator will call the survivors. The first week call will begin with the assessment of symptoms using the GSDS (described in the Measures section). For each symptom rated at 4 or higher on a 0-10 scale of severity, the survivors will be referred to the SMSH for symptom self-management. The threshold of 4 was selected based on the NCCN guidelines for symptom monitoring and management83 and used successfully in past work. [75,76,81,82,89] When a symptom is rated at a 7 or higher on the 0-10 scale, patients will be asked to contact their health care provider. During weeks 2-12, calls will begin with assessment of SMSH use since the last call (intervention enactment), followed by the administration of the GSDS and referral to the SMSH for any above threshold symptoms. Calls will last approximately 10 minutes.

b). Telephone Interpersonal Counseling Intervention (TIP-C). The 8-week TIP-C intervention is detailed in Table 3 and social workers with a master's degree and psychiatric-mental health and oncology expertise deliver TIP-C weekly. During weekly contacts, the counseling targets social support behaviors using interpersonal communications techniques. Interpersonal communication facilitates processing stressful affective reactions to a cancer diagnosis and treatment, marshalling instrumental support for assistance with roles and functions, informational support for advice and information, and appraisal support for gauging and adjusting to the stressor. Interventionists can personalize the counseling intervention for the specific needs or interests as expressed during sessions while still adhering to a structured protocol. For example, one survivor may need to focus on depression and family issues (e.g., role transitions such as job loss) rather than on anxiety and resource issues (e.g., transportation, lack of insurance). This approach is consistent with cancer survivorship care recommendations [181] and recent evidence showing that improved psychological well-being occurs when an intervention addresses practical resource needs (e.g., finances).[182]

	Table 3: TIP-C Intervention
1	Introduction to protocol. Counseling, symptoms of depression, anxiety, stress, psycho-education, interpersonal formulation (session slightly longer).
2	Symptoms and interpersonal relationships, communication with key targets, modeling of communication processes with family, friends, and health care providers (HCP).
3	Role transitions, effective social skills for coping/adapting to cancer, role playing interpersonal interactions, accessing resources
4	Role disputes/role transition, focus on communication with family, friends and HCP. Homework activity will focus on communication, developed individuality for each participant and completed between sessions.
5	Review homework assignment. Problematic communication patterns with others, role modeling successful communication with others.
6	Social support, barriers to seeking and securing social support. Homework assignment is an individualized activity.
7	Progress with cancer survivorship. Review homework assignment. Stress and coping strategies, sources of satisfaction. Homework assignment: Increasing pleasant events.
8	Termination of counseling, review successes, reviews social support, stress and coping strategies. Future planning recommendations for follow-up treatment (e.g. antidepressants or continued counseling), framing successes and failures. Discuss options and referrals as needed. Resources available locally and nationally for survivors and their families, including financial, insurance[172] and legal information[173] (session slightly longer).

8.0 STATISTICAL CONSIDERATIONS

Analysis Plan for answering objectives including endpoint definitions, patient accrual objectives, and estimated duration of study. This section should be developed in consultation with appropriate biostatistician.

Potential Covariates and Future Tailoring Variables. Demographic characteristics include survivors' age, education, work, ethnicity, race, acculturation, and marital status, and language of intervention delivery. Receipt and enactment of intervention strategies are measured during weeks 1-12. Receipt is the number of completed weekly sessions. Enactment of the SMSH strategies is assessed at the beginning of calls during weeks 2-12. Enactment of the TIP-C will be measured by tracking the implementation of behaviors discussed and completion of the assigned homework as documented in counselor's field notes for each session. Survivors' chart data will include radiation, surgery, chemotherapy, targeted or hormonal therapy (dose, type, dates received), co-morbidities, cancer site and stage, and medications (e.g., supportive agents for symptoms) corresponding with the time-on study.

Scientific Rigor and Transparency. The scientific rigor of this study is ensured by the randomized design and complete inclusion/exclusion criteria defining the population to which findings would be generalizable. We also have a reproducible manualized protocol for the interventions, tracking of intervention fidelity, dose, receipt and enactment, use of measures with solid evidence of reliability and validity, blinding of data collectors and transparent assessment and statistical analysis plans including attention to biases and the missing data.

Sex as a biological variable. We expect more than 50% of the sample to be female (Human Subjects section). We will consider sex as covariate and a potential future tailoring variable in the exploratory aim.

Analytic Methods

Data management. Data will be entered into the secure web-based database that will be accessible to recruiters, interveners and interviewers. The RA will perform quarterly quality assurance checks of the data, supervised by Dr. Sikorskii. De-identified data will be transferred into SAS 9.4 for analyses. Distributions of outcomes and potential covariates will be summarized. Outliers will be investigated by inspecting the residuals, and models described below will be fit with and without outliers to examine

their influence on the results. Sensitivity to the degree of personalization of TIP-C (see C7d) will be examined by relating it to the primary outcome at week 13 for those who received this intervention.

Attrition Analyses and Handling of Missing Data. Attrition will also be compared between each pair of randomized groups. In addition, we will compare characteristics of those who completed the study with those who did not within their designated group to inform the generalizability of findings. The regression techniques described below allow for missing at random (MAR) mechanism.199 If patterns of missing data indicate potential not missing at random (NMAR) mechanisms, then models describing missing mechanisms will be considered (e.g., pattern-mixture models),[200,201] and sensitivity analyses will gauge the robustness of the results.

Primary Analysis. The intent-to-treat principle will be followed.
Aim 1. Hypothesis 1 will be tested using statistical model #1 that relates repeated measures of the survivor primary outcome y (summed severity index) to the group assignment variable $x1$, outcome at baseline $x2$, time entered as a class variable to model potentially non-linear patterns, and other covariates. Because the symptom severity index is expected to follow a right-skewed distribution, this model will be fit as a generalized linear mixed effects (GLME) model with gamma distributed errors. The main effects of the group variable $x1$ (average difference over time between groups created by the first randomization) will be tested. While summed symptom severity is a succinct outcome summarizing 15 symptoms, it has its drawbacks that will be overcome with the next analysis that focuses on specific symptom responses (secondary outcomes). The unit of analysis will be symptom case. Cases reaching moderate or severe at baseline or any time during weekly calls will be analyzed. Symptom responses and times-to-response defined under measures will be analyzed using methodology described by Sikorskii et al.[97] Patient symptom responses are treated as multiple events, and associations among responses to multiple symptoms nested within patients will be accounted for in the GLME model with binomial errors. Marginal Cox proportional hazard models with a robust sandwich covariance matrix estimate implemented in PHREG procedure in SAS[203,204] will be employed for the analysis of multiple times to response nested within survivor. Symptom- and survivor-level covariates will be included in the model, and different intervention effects for different symptoms will be evaluated. For randomized arms, dummy variables $x1,1, \ldots x1,15$with two levels (corresponding to randomized group assignment) will be created to model possibly different effects of interventions across 15 symptoms. With the marginal Cox model, times to 15 types of events (specific symptom responses) will be considered. First, the equality of beta coefficients for the study group across symptoms will be tested. If, based on this test, the effects of the study group are different across symptoms, then tests for the equality of each coefficient to zero will yield the tests of the intervention effect on each of the 15 symptoms. If the effects are not significantly different across symptoms, then the model will be modified to include only one two-level group variable; the test of equality of its coefficient to zero will yield the formal test of Hypothesis 1.
Hypothesis 2. The strategy described under the analyses for Hypothesis 1 will be implemented for the repeated outcome measures during weeks 5-13 that will be related to group assignment from the second randomization, summed symptom severity during week 4, time, and covariates. Analyses for symptom responses and times to response will also be similar to those described above except we will use weeks 5-13 instead of weeks 1-13, and groups created by the second randomization.
Hypothesis 3. To test for mediation, study group will be treated as the independent variable and each of the potential mediators (one at a time) will be tested for their effect on the primary outcome variable at week 13, controlling for its baseline value. We will use a bias corrected bootstrapping analytic strategy[205, 206] based on 5000 bootstrap samples to estimate confidence intervals around the indirect effect of study group on the primary outcome, through the mediator. To establish mediation, the 95% confidence interval around the indirect effect must not include 0.

Aim 2. Benchmarking of the outcomes produced by three intervention sequences against the low need group will be accomplished using a 4-level variable (0=low need referent level, 1=SMSH alone for 12 weeks, 2=TIPC+ SMSH for 8 weeks then SMSG alone for 4 weeks, 3=SMSH alone for 4 weeks then TIP-C+SMSH). We will be repeating the analyses described under Hypotheses 1 and 2 with this new variable and data from weeks 4 and 13. Because the low need group was created by screening and not by randomizations, there will be no causal conclusions drawn from the comparisons of levels 1-3 to the referent level. However, these comparisons will help gauge the clinical significance of the improvements due to the interventions in the high need group.

Exploratory Aim. The characteristics of responders will be compared to those of non-responders using t-tests, chi-square or Fisher's exact tests. Characteristics found to differ, along with mediators and other covariates listed in section C9d will be further considered as potential future tailoring variables. The optimal intervention sequences will be formed by identifying tailoring variables and determining the optimal decision rule ($d1$, $d2$) specifying the first and second intervention to achieve optimal outcome given the values of the tailing variables. The analysis approach to this aim follows the Q-learning optimization method175,207-209 implemented in SAS PROC QLEARN.[210,211] The Q-learning algorithm proceeds from right to left in Figure 1, i.e., backwards from the last decision to the first. Two Q-functions will be considered. The function $Q2(H2) = E[Y2|H2]$ is the expectation of the second stage outcome $Y2$ given history after 2 stages (weeks 1-13, denoted by $H2$): survivor characteristics, outcomes observed during weeks 1-13 and interventions received. The function $Q1(H1) = E[Y1 + \max Q2(H2)]$ uses history through the first intervention stage $H1$, weeks 1-4.The conditional expectations in the Q-functions will be estimated from the mixed model analyses for the summed severity index, and the optimal decision rules will be found using backward induction by optimizing these functions.[212,213] The resulting tailored decision rules can then undergo formal testing in a future confirmatory RCT.

Potential Difficulties/Limitations and Alternative Approaches

Table 4 shows the project timeline. Potential problems from recruitment and retention will be minimized by the use our previous methods yielding high retention rates with no differential attrition between conditions. Potential problems in intervention delivery are minimized by implementing protocols for intervention fidelity. There are no high-risk aspects of this trial, and all procedures are non-invasive. We recognize that in addressing depression our efforts might inadvertently produce detrimental psychological responses. Should this occur, our experienced interventionists will refer the survivor to mental health services. Because randomizations may not account for all possible error sources, we will adjust for baseline values of outcomes in the analysis to provide added control over pre-intervention influences. All outcomes and hypotheses are stated a priori. In the exploratory analyses, multiple testing will be addressed by employing the Benjamini- Hochberg or Hochberg adjustment[214-216] to control the false discovery rate.

Table 4: Timeline of the Project	**Year 1**				**Year 2**				**Year 3**				**Year 4**			
Quarters:	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
IRB approval	X															
Update manuals; hire/train staff	X	X														
Enroll subjects; deliver intervention; collect data			X	X	X	X	X	X	X	X	X	X	X	X		
Complete medical record audits				X	X	X	X	X	X	X	X	X	X	X	X	
Set up/conduct analyses; annual/final reports	X	X		X			X	X			X	X	X	X	X	X

9.0 STUDY TIMELINE

List of all parameters and required intervals for observations, measurement of outcomes, intervention and intervals at which it is given.

Table 5 represents the protocol using the SMART design schema in Figure 1. Forms required of protocol include: Baseline and week 13 follow-up questionnaires (T2), debriefing and satisfaction questionnaire (T2), GSDS, SMSH form (internal only), TIP-C form (internal only).

Table 5: Protocol

<table>
<tr><th>Time</th><th colspan="3">Actions</th></tr>
<tr><td>Enrollment</td><td colspan="3">Recruit, Enroll, Consent, Set up Baseline Assessment</td></tr>
<tr><td>Baseline (week 0)</td><td colspan="3">Baseline Assessment with all questionnaires by Data Collector-may or may not be interventionist assigned.
Data Collector completes notifies Project Coordinator that interview has been completed.</td></tr>
<tr><td>Screening and stratification into low versus high need (week 0)</td><td colspan="3">Project Coordinator will look up need status in the database. Logic programmed in RedCap based on no co-morbidity (Bayliss tool) and CES-D score in baseline interview:
<u>Low need benchmark stratum:</u> no or some comorbid conditions and NO depression (CESD <16).
<u>High need stratum:</u> 1 or more comorbid condition and CESD of 16 or higher OR 2 or more comorbid conditions (not including cancer) regardless of CES-D score.</td></tr>
<tr><td></td><td>Low need benchmark stratum</td><td colspan="2">High need stratum</td></tr>
<tr><td></td><td rowspan="2"></td><td colspan="2">Project Coordinator will run randomization program to allocate high need survivors to either SMSH or SMSH+TIP-C.
Interventionist assigned and will set up first session, mark calendar for the other sessions over 12 weeks</td></tr>
<tr><td></td><td>SMSH in the first randomization</td><td>SMSH+TIP-C in the first randomization</td></tr>
<tr><td>Week 1</td><td>Nothing</td><td>Session 1- On the Handbook form, document GSDS symptoms and chapters referred.
Set up/confirm next appointment.</td><td>Session 1- On the Handbook form, document GSDS symptoms and chapters referred.
Conduct TIP-C per protocol. Complete the TIP-C form.*
Set up/confirm next appointment</td></tr>
<tr><td>Week 2</td><td>Nothing</td><td>Session 2- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Set up/confirm next appointment.</td><td>Session 2 - On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred.</td></tr>
</table>

			Conduct TIP-C per protocol. Complete TIP-C form.* Set up/confirm next appointment.
Week 3	Nothing	Session 3- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Set up/confirm next appointment.	Session 3- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Conduct TIP-C per protocol. Complete TIP-C form.* Set up/confirm next appointment.
Week 4	On the week 4 low need group form, document symptoms using GSDS (data collector, not intervener).	Session 4- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Set up/confirm next appointment. Remind survivor they may be continuing in this intervention or switched to SMSH+TIP-C for 8 more weeks (see protocol). Will have to call back and set up/confirm next appointment.	Session 4- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Conduct TIP-C per protocol. Complete TIP-C form*. Set up/confirm next appointment.
After Week 4- 2nd randomization will occur	No change	Project Coordinator to determine survivor's response on depression. In the baseline interview, use GSDS rating of depression to determine if depression was mild (0-1), moderate (2-3) or severe (4+). Then determine if depression was mild/moderate/severe at the last completed of weeks 1-4. If depression was mild at baseline and last week, then response. If depression was moderate/severe at baseline then became one category lower at last week, then response. Otherwise non-response (depression did not improve by one or more categories or did not stay mild). If response, continue with SMSH only. If non-response, Project Coordinator will re-randomize to either continue with SMSH only, or add TIP-C beginning with	

		week 5.		
		SMSH only continued (response or randomized in the second randomization)	**SMSH+TIP-C in the second randomization**	**SMSH+TIP-C in the first randomization**
Week 5	Nothing	Session 5 - On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Set up/confirm next appointment.	Session 5- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Start TIP-C per protocol (session 1 of TIP-C. Complete the TIP-C form.* Set up/confirm next appointment.	Session 5- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Conduct TIP-C per protocol. Complete TIP-C form*. Set up/confirm next appointment.
Week 6	Nothing	Session 6 - On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Set up/confirm next appointment.	Session 6- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Conduct TIP-C per protocol (session 2 of TIP-C). Complete TIP-C form. * Set up/confirm next appointment.	Session 6- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Conduct TIP-C per protocol. Complete TIP-C form.* Set up/confirm next appointment.
Week 7	Nothing	Session 7 On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Set up/confirm next appointment.	On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Conduct TIP-C per protocol (session 3 of TIP-C). Complete TIP-C form.* Set up/confirm next appointment.	Session 7- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Conduct TIP-C per protocol. . Complete TIP-C form.* Set up/confirm next appointment. Complete the TIP-C

				form.
Week 8	Nothing	Session 8- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Set up/confirm next appointment.	On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Conduct TIP-C per protocol (session 4 of TIP-C). Complete TIP-C form*. Set up/confirm next appointment.	Session 8- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Conduct TIP-C per protocol. Closure of TIP-C. Complete the TIP-C form. * Set up/confirm next appointment to continue with SMSH only for the next 4 weeks.
Week 9	Nothing	Session 9- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Set up/confirm next appointment.	Session 9- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Conduct TIP-C per protocol (session 5 of TIP-C). Complete the TIP-C form. * Set up/confirm next appointment.	Session 9- Document what was done on Handbook form, Assess with GSDS, document symptoms, handbook chapters referred. Set up/confirm next appointment
Week 10	Nothing	Session 10- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Set up/confirm next appointment.	On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Conduct TIP-C per protocol (session 6 of TIP-C). Complete the TIP-C form.* Set up/confirm next appointment.	Session 10- Document what was done on Handbook form, Assess with GSDS, document symptoms, handbook chapters referred. Set up/confirm next appointment

Week 11 All interveners should notify Project Coordinator when session 12 is scheduled so that interviewer is assigned to set up week 13 interview.		Session 11- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Set up/confirm next appointment.	Session 11- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Conduct TIP-C per protocol (session 7 of TIP-C). Complete the TIP-C form. *Set up/confirm next appointment.	Session 11- Document what was done on Handbook form, Assess with GSDS, document symptoms, handbook chapters referred. Set up/confirm next appointment
Week 12 Set up appointment for final assessment	Data collector to call and set up T2 assessment for next week.	Session 12- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Do closure as is final session. Thank participant for participation. Remind participant that someone (give name if have) will call for follow-up interview in about a week.	Session 12- On the Handbook Form, document what was done, GSDS symptoms, and handbook chapters referred. Conduct TIP-C per protocol (session 8 of TIP-C). Complete TIP-C form.* Closure as is final session. Thank participant for participation. Remind participant that someone (give name if have) will call for follow-up interview in about a week.	Session 12- Document what was done on Handbook form, Assess with GSDS, document symptoms, handbook chapters referred. Closure as is final session. Thank participant for participation. Remind participant that someone (give name if have) will call for follow-up interview in about a week.
Week 13	On the T2 Questionnaires, final Assessment with all Questionnaires-data collector Document additional debriefing questions (part of the T2 questionnaires).			

10.0 DATA SAFETY AND MONITORING PLAN

Describe plans to monitor adherence to study protocol, integrity of data collection and intervention delivery. Include any plans regarding project quality assurance.

Data Safety and Monitoring Plan. This behavioral intervention study meets the definition of a clinical trial. Data and Safety Monitoring will be accomplished through multiple approaches:

Institutional Review Board (IRB) - All procedures related to data collection and safety will be approved by the University of Arizona (UA) Health Sciences Center IRB and by the independent Arizona Cancer Center Office of Clinical Trials. Processes will be established to guide collection, transfer and storage of data and training of staff to ensure data safety. Quality assurance (QA) reviews of data and staff will be performed as described below.

1. *Security Procedures for Collection, Transfer and Storage of Electronic Data.* Electronic files will consist of enrollment data, survey data at two time points, symptom data collected during the weekly calls, interventionist call data for survivors allocated to TIP-C + SMSG and survivor's medical record data (collected at enrollment and during medical record audit after survivors complete their 13 week interviews). First, enrollment data with identifiers will be stored separately from the study data. Second, all computers that will store data at the central location will be password protected. The system will have a secure login along with audit control mechanisms to meet the HIPAA guidelines. Third, servers will utilize state-of-the art security processes. Electronic copies of forms, such as the consent or HIPAA authorization form will be stored on a secure dedicated server with appropriate firewalls. The system will use encryption (SSL certificate) to transfer data between the machines. This technology is the same as that used for online e-commerce applications to protect consumer information. Servers are scanned for viruses and systems are in-place to detect attempts at unauthorized entry. All transactions to the database are stored in archive logs as re-do data and are accessible to enable quick recovery of all data should the need arise. Backup files are written nightly to back up servers.

2. *Security Procedures for Collection, Transfer and Storage of Paper Data.* Paper files will consist of consent and authorization forms and medical record audits. Paper copies of all forms will be faxed to the central study office for data entry. Faxed copies of medical records will be retained in locked storage cabinets at UA accessible only to study personnel.

3. *Training of Staff. R*ecruiters will follow UA institutional processes for enrollment of patients to clinical
trial(s). Training by the study Coordinator will occur in order to ensure recruiters understand eligibility criteria, study design and goals. Training will emphasize strategies to maximize enrollment and retention of minority participants. Additionally, training will occur to assure recruiters understand the function and importance of data gathered during the medical record audit at enrollment. Training will include completion of simulated cases. Booster training sessions will be scheduled as needed.
Interviewers/Data Collectors - will be carefully instructed and trained in appropriate interviewing techniques and will receive regular monitoring by the study Coordinator to ensure the ethics of research and scientific integrity and protection of confidentiality. Participants are asked prior to each interview if they want to continue and are given a toll-free number to contact UA if they have questions or concerns.
Interventionists- TIP-C interventionists will receive 24 hours of education, augmented by additional books and articles, about cancer diagnosis and treatment, psychological distress, and interpersonal counseling techniques with training protocols developed in previous studies (Appendix C). The interventionists will listen to 8-10 hours of counseling sessions recorded for training purposes. Drs. Badger and Segrin will conduct interventionist training that will continue until the interventionists are rated as achieving > 90% on protocol implementation. Annual re-training will occur throughout the study**.**
Medical Record Auditors – will be the recruiters or are employees of each recruitment site with oncology experience but trained by the study Coordinator on collection of data for this study. Training will target job descriptions, and roles and responsibilities of group members and will consist of 1) an overview of project objectives, theoretical framework, and research design and rationale, 2) background and training on collecting data free from bias, 3) information on scale and item response

issues; 4) protection of human patients and confidentiality issues; and 5) data and intervention monitoring and quality assurance procedures. Activities for training will consist of lectures, discussion,

4. *Monthly Meetings* – Monthly meetings with all research staff will be conducted to review accrual, attrition, discuss problems and/or concerns and ensure everyone understands and is following the protocol.

5. *Quality Assurance Activities for Project Staff* – Quarterly quality assurance (QA) will involve engaging in good data management activities. Procedures that include checking the integrity of data storage and examining frequency distributions to look for anomalies such as an excessive number of "don't know" responses or problems with skip patterns will be in place.

Recruiters – Enrollment data will be monitored monthly for completeness and consistency. If any missing data are identified, the completion of missing fields will be requested and questions clarified during quarterly QA review of the data.

Interviewers - The level of quality of each interviewer and the interview process are monitored monthly by the study Coordinator and Investigators. A cadre of well-trained interviewers at UA is available and used by this team in previous studies. Early in the study, until proficiency is reached, the interviewers digitally record every interview for QA. Following initial training, interviewers will be required to record and submit 1 interview each month for review. There is no identifying information recorded. Booster training sessions are held with interviewers on a scheduled basis. Written feedback on the quality of the telephone interview is provided to all interviewers following review of each recording.

Interventionists - All sessions are digitally recorded and about 10% randomly reviewed throughout the study to maintain quality, with written and verbal feedback given to the counselors. Drs. Badger and Segrin will supervise the intervention quality control activities. Through weekly case supervision, we will maintain fidelity of the intervention and counselor adherence to protocols. We will evaluate adherence (number required elements discussed/ total number of elements). Drs. Badger and Segrin will listen to all sessions in English from the first 5 dyads (40 hours of supervision) and then randomly review 10% of sessions throughout the study. A bilingual counselor will review sessions in Spanish using established protocols as in past studies. Counselors who do not maintain 90% adherence will not be given new cases until retraining has occurred, and Drs. Badger or Segrin will assume responsibility for those existing cases. Following retraining, 5 dyads will be monitored to ensure that >90% adherence is achieved and then we will return to randomly selected monitoring for quality control. Anyone unable to adhere to the standardized protocols is replaced after a second retraining.

Data - Quality assurance reports will be prepared on a quarterly basis by the statistical research assistant supervised by Dr. Sikorskii and reviewed by the study Coordinator and investigative team. That is, for the internal audit, someone independent of the data collector will check the data. Data from 10% of the recorded interviews and intervention sessions compared to database entries. The acceptable error rate is 0.3 %, i.e., 3 out of 1,000 fields. All errors are corrected during the QA check. Dr. Sikorskii will oversee preparation of the data report distributed to all investigators at least 5 days before the scheduled meeting. The report will include the summary of cumulative and quarterly accrual, randomization, cumulative attrition, and attrition by study group, gender, and race/ethnicity, adverse events and serious adverse events, data completeness and quality, and study Consolidated Standards of Reporting Trials (CONSORT) chart. Reports will also inform the Investigators about missing, invalid, or inconsistent data on selected key variables. For the external oversight, Dr. Jessica Rainbow who is not involved in the study has agreed to participate in QA meetings.

6. *Identification of Adverse Effects*- The following will be considered serious adverse events (SAE): death, attempted suicide, major depression, breach of confidentiality. Death, attempted suicide and major depression would not occur as a direct result of study interventions, however, could be encountered during implementation of this study due to the inclusion criteria of cancer survivors. A breach in confidentiality may result from participation in this study. The investigators have successfully

trained staff to monitor and protect confidentiality of participants in large research studies conducted over the past two decades. Similar training strategies will be incorporated for training of staff in this study. Additionally, all research staff will complete the human subjects and HIPAA certification training.
The following will be considered adverse events (AE): severe symptoms requiring hospitalization or urgent care. Again, severe symptoms are not expected to result from participation in this study but may result from cancer, its treatment or other existing comorbid conditions.

Averse events and serious adverse events may be identified during implementation of the experimental protocols and are monitored by the Investigators in several ways.
Interviewers: Interviewers may identify both serious adverse events and/or adverse events during completion of telephone interviews or telephone calls to schedule telephone interviews.
Interventionists: The interventionists may identify both serious adverse events and/or adverse events during their telephone contacts with the participants.

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14.0 APPENDICES

APPENDIX I – FORMS

- Recruitment Script
- Contact Form (internal document)
- Telephone survey (baseline and 13-week follow up)
- Debriefing and satisfaction
- Medical Record Audit Form (internal document)

APPENDIX II – STUDY INFORMATION

- Study Brochure
- Study Flyer
- Study webpage

APPENDIX III – INTERVENTION INFORMATION

- Symptom Management Toolkit
- Weekly GSDS script
- Handbook form (internal document)
- TIP-C form (internal document)