SCIENTIFIC REVIEW COMMITTEE

Title: Improving Informal Caregivers' and Cancer Survivors' Psychological Distress, Symptom Management and Health Care Use

KEY PERSONNEL

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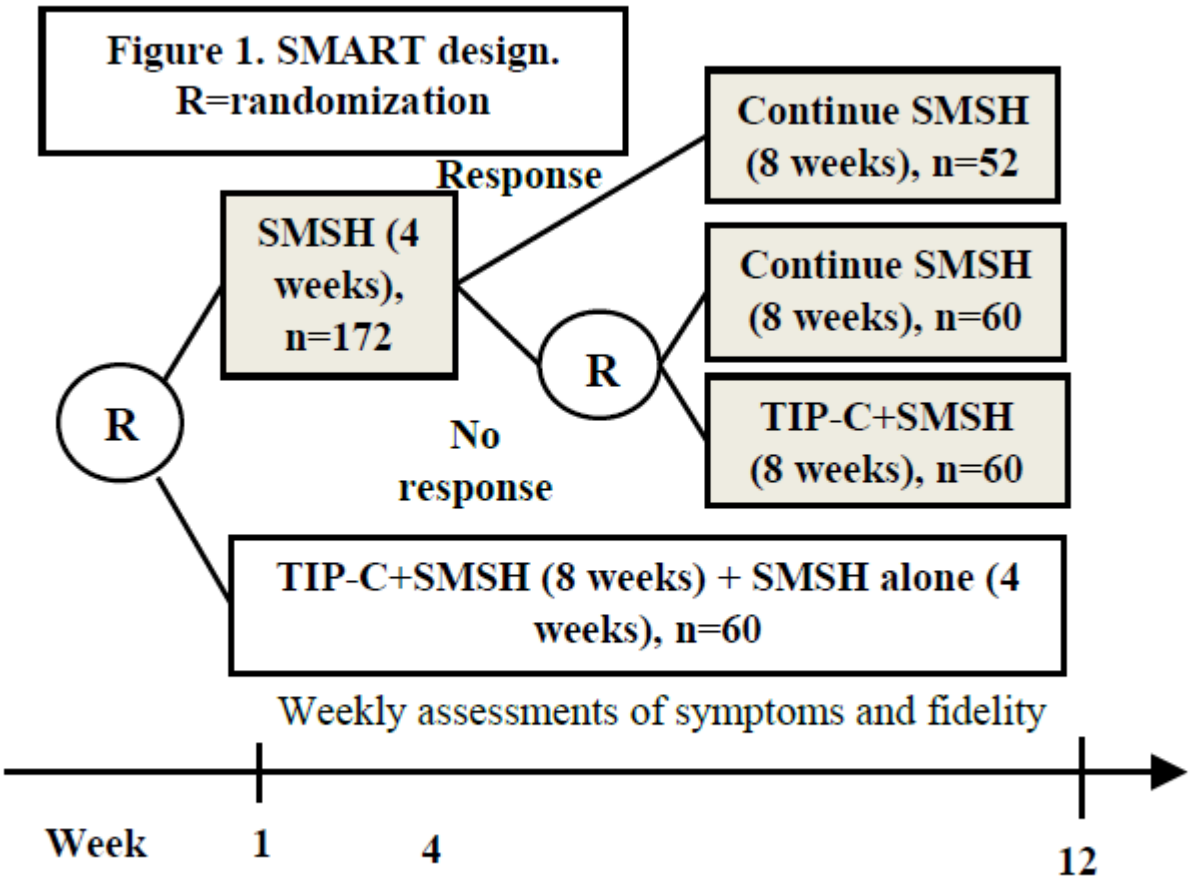
SCHEMA OR FLOWCHART

Insert schematic or diagram outlining study design and procedures



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.

Informal Caregivers of Cancer Survivors. Informal caregivers are people within the survivor's social network, related by blood or emotional attachment, who provide emotional, informational and/or instrumental support.[52] The value of this unpaid labor force of 44 million caregivers in the United States[53] is estimated to be at least $306 billion annually,[54,55] with 5.7 million caregivers providing care to cancer survivors.[56] Caregivers of cancer patients become involved in complex care activities[57] for an average of 14 months.[58,59] A shift to patient-centered care is facilitated by engaging the caregivers and requires the understanding of survivors' and caregivers' outcomes resulting from such engagement.[60,61] Caregivers experience a range of psychological problems, disruption of daily routines, financial burdens, and role changes that accompany the care recipient's cancer diagnosis and treatment.[62-64] Caring for the survivor often has negative consequences to the caregiver's family resources and health.[65,66] Caregivers have poorer physical health than those in the general population, reflected by higher prevalence of arthritis, chronic back pain, and heart disease.[67] Between 30-50% of caregivers experience increased psychiatric morbidity, fatigue, sleep impairment. [68-70] Psychological distress among caregivers is often present at levels equal to or greater than among cancer survivors.[40,71-81] Risk of these morbidities is particularly high among caregivers who are female,[82-84] less educated,[85] younger in age,[86] and who are caring for younger adult survivors.[87,88] These findings explain increased use of health care services among caregivers of those recently diagnosed with cancer.[89,90]

Meaningful involvement in the survivor's care may also have a positive impact on caregivers' health,[91-94] which improves the quality of care they provide to the survivors.[95-98] For these reasons, interventions providing caregivers with tools such as the SMSH are highly valuable.[99,100] Further, psychosocial interventions that directly improve caregivers' health,[101] reduce psychological distress and address problem-solving and communication skills,[102] are also potentially beneficial to survivors and their caregivers. The proposed research will deliver psychosocial (TIP-C) and educational (SMSH) interventions and test their optimal sequencing for survivors with known levels of distress and symptom severity as well as their impact on their caregivers who often experience distress and associated other symptoms (e.g., poor sleep, fatigue).

Symptom burden in cancer survivors. Physical and psychological symptoms are aggravated while cancer survivors are in treatment.[103,104] Survivors' symptom burden[105-112] is often the primary reason for altering or stopping chemotherapy[113,114] leading to suboptimal treatment at the very least,[115-117] and life threatening recurrence or metastasis at the extreme.[118,119] The prevalence of specific symptoms (e.g., fatigue, pain, depression, anxiety, disturbed sleep, nausea and vomiting, neuropathy)[120-125] varies by cancer diagnosis, treatment type, gender, ethnicity and age,[98,99] variables that will be empirically tested as potential tailoring factors in decision rules that will be formulated in this research. The number of symptoms reported by cancer survivors can be as high as 14.[126] [127] Approximately 30% of cancer survivors report psychological distress (depression and anxiety). Major depression occurs in approximately 16%, and subthreshold depressive disorders occur in 22% of cancer survivors during treatment.[28] These prevalence rates are about 3 times higher than in the general population. Even when depression and anxiety do not meet threshold for clinical diagnoses, these symptoms are still associated with significant health impairments, yet are highly treatable,[128,129] and will be in this trial, potentially saving healthcare costs and improving outcomes. Further, in our past studies, Latinas with breast cancer reported a higher number and more symptom burden/distress than did non-Hispanic white women with similar diagnoses.[31] Therefore, we will enroll an ethnically diverse sample (includes 30% Hispanic/Latino participants) in this trial to address a significant symptom management need. Given the increasing population of Hispanic cancer survivors, providing and testing an intervention in the participant's primary language could have national significance. A series of longitudinal studies[130-133] including those conducted by this team[130,131], found an association between increasing symptom prevalence and poorer physical and emotional functioning. Our team's past work[134] and that of others[135] documented the associations between reductions in symptoms and lower number of hospitalizations, office and ED visits.[10] The proposed interventions are significant because they will address the multiple symptoms experienced by survivors during treatment and the associated health care service use.

2.0 OBJECTIVE(S)/SPECIFIC AIMS

Purpose and specific aims of the study.

Informal caregivers, typically family members or friends, provide more than half of the care needed for the 5.7 million cancer survivors in the United States, often with negative health consequences. At least 30% of survivors and their caregivers report psychological distress (depression and anxiety) and such distress may interfere with optimal symptom management. This study will support both members of the survivor-caregiver dyad in the management of the survivor's cancer- and treatment-related symptoms and the dyad's psychological distress.

Design: We will use the sequential multiple assignment randomized trial (SMART) design, a newer adaptive design. The SMART moves beyond a traditional RCT to a precision approach to determine the right treatment at the right dose with the right sequence for the right survivor-caregiver dyad. We will use two evidence-based interventions: Symptom Management and Survivorship Handbook (SMSH) and Telephone Interpersonal Counseling (TIP-C). While we have established the overall efficacy of these interventions, but individuals differ in responses. When an intervention does not initially work, clinic logic is to either extend the timeframe or prescribe a different intervention. Yet, such alternatives are seldom tested nor evidence-based. However, they will be in this study.

Sample: We will enroll 298 survivors with elevated depression or anxiety who are undergoing chemotherapy or targeted therapy for a solid tumor and their 298 caregivers.

Procedure: Dyads will be initially randomized to SMSH alone or TIP-C +SMSH. If the survivor's elevated depression or anxiety does not respond to SMSH alone by week 4, dyads will be re-randomized to continue with SMSH to give it more time or to TIP-C+SMSH. Outcome data will be collected at baseline, weeks 13 (post-intervention) and 17 (follow-up). Assessments during weeks 1-12 will document changes in symptoms, intervention receipt, enactment and fidelity.

Specific aims: **1)** Determine if dyads in the TIP-C+SMSH as compared to the SMSH alone group created by the first randomization will have: a) lower depression, anxiety, and summed severity of 13 other symptoms at weeks 1-12, 13, and 17 (primary outcomes); b) lower use of healthcare services (hospitalizations, urgent care or emergency department [ED] visits) during17 weeks (secondary outcomes); c) greater self-efficacy, social support, and lower caregiver burden during weeks 13 and 17 (potential mediators). **2)** Among nonresponders to the SMSH alone after 4 weeks, determine if dyads assigned to TIP-C+SMSH as compared to the SMSH alone group created by the second randomization will have better primary and secondary outcomes and potential mediators at weeks 5-12, 13, and 17. **3)** Test the interdependence in survivor's and caregiver's primary and secondary outcomes. **4)** Determine which characteristics of the dyad are associated with responses to the SMSH alone during weeks 1-4 and optimal outcomes for the dyad during weeks 1-12, 13 and 17 so as to determine tailoring variables for the decision rules of individualized sequencing of interventions. Findings will be used to improve symptom management and reduce distress in survivor-caregiver dyads.

3.0 SAMPLE ELIGIBILITY CRITERIA

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

Inclusion criteria for the survivors are: **1)** age 18 or older; **2)** undergoing chemotherapy, hormonal therapy, or targeted therapy for a solid tumor cancer; **3)** able to perform basic activities of daily living; ***4) cognitively oriented to time, place, and person (determined by recruiter)***; **5)** reporting severity of >2 on depression or >4 on anxiety using a 0-10 standardized scale; **6)** able to speak and understand English or Spanish; **7)** access to a telephone and **8)** has a caregiver who can be in any relationship role (e.g., spouse, sibling, parent, friend) who can participate with them.

Exclusion criteria are: **1)** diagnosis of a psychotic disorder in the health record; **2)** nursing home resident; **3)** bedridden; **4)** currently receiving counseling and/or psychotherapy. Inclusion criteria for the caregivers are: **1)**

age 18 or older; **2)** able to speak and understand English or Spanish; **3)** access to a telephone; 4**)** not currently receiving counseling and/or psychotherapy; and **5)** not currently treated for cancer.

The advantages of these inclusion criteria are in study generalizability. Solid tumors have been selected because cancer- and treatment-related symptoms can be effectively managed in this population with the two interventions (see section C2). Site of cancer and other prognostic factors will be controlled in randomization (see C7). Thus, groups compared in study hypotheses will be balanced on disease and treatment characteristics. The cut-offs of >2 on depression and >4 on anxiety indicate their presence at moderate or severe levels based on established interference-based cut-points.[224] The need to screen on depression and anxiety is premised on a meta-analysis that psychosocial interventions are most beneficial for those with elevated distress.[225,226] By allowing survivors to select their own caregivers, findings would be generalizable to the cancer survivor population who may be single or rely on other people for support. The exclusion of caregivers currently treated for cancer will preserve the distinguishability of the "survivor" and "caregiver" roles within the dyad. Our prior research indicates that participation in counseling and/or psychotherapy for either dyad member is rare during survivors' treatment. These exclusion criteria will not substantially limit the population but will eliminate potential confounding of the intervention effects with extraneous influences.

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.

Sample. We will recruit 298 dyads (see below for power), allowing for 22% attrition, for a final post-attrition sample of 232 dyads available for analysis. 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. Of the estimated 35,810 newly diagnosed cases of cancer[227] in AZ in 2017, the majority were solid tumors. Conservatively, we will have easy access to about 3000 survivors with our existing sites, of which approximately one third (n=1000) should satisfy the inclusion criteria. Following the initial recruitment contact, we anticipate about 10% will consent to participate, thus we can recruit 100 dyads per year. Given this team's past successful recruitment at the UACC and community sites (letters of support), the proposed study will easily meet the recruitment goal of 99 dyads each year of the 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 needed number of consenting dyads. To power the comparisons on primary outcomes for the groups created by the second randomization (Aim 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 1) to conservatively estimate sample size requirements. We further adjusted this effect size for the reduction in error variance due to 10 repeated measures of primary outcomes. In past studies, Pearson correlation coefficients between pairs of repeated measures of depression, anxiety and summed severity of other symptoms 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.

Moving from left to right in Figure 1 (schematic), 120 dyads from two groups created by the second randomization will be non-responders to the SMSH alone. From past work, response rate to the SMSH on depression and anxiety was approximately 30%,[228] therefore 120 non-responders will be 70% of 172 randomized to the SMSH alone in the first randomization. The comparison of these 172 to 60 dyads allocated to the TIP-C+SMSH in the first randomization will have power of 0.95 to detect the effect size of 0.54 (adjusted for the repeated measures) in testing the hypothesis associated with Aim 1. The tests of mediation and interdependence effects in Aim 3 will have an even greater power because of further reduction in error variance. Aim 4 is exploratory, thus formal power considerations are not applicable. In summary, the total

required post-attrition sample size for all specific aims is N=232. To account for 22% attrition based on past work, we will need 298 dyads to consent.

Recruitment and retention of participants.

Accrual. Recruiters have research roles and do not provide direct care at the sites. They will approach survivors during clinic visits and explain the study. Survivors can choose to consent at that time or take the packet home to discuss with their caregivers. Recruiters will follow up during a clinic visit or by phone to further explain the study, answer questions, and discuss the study with caregivers. If the survivor or caregiver give verbal consent over the phone, the participant will return the signed consent forms with witnessed signature in a postage paid envelope. If the consent forms are not returned within one week, the recruiter will call the participant to ask that the signed consent forms be mailed if they wish to participate.

Recruiter training. The study Coordinator will conduct recruiter training that includes didactic information, role-playing, and return demonstration of recruiting per script. Recruiters will introduce the study to survivors: 17-week study duration, randomizations to TIP-C+SMSH versus SMSH alone to help manage symptoms, 12 weekly calls and three interviews, no cost to study participation, risks/benefits, and incentives.

Subject incentives. We will provide gift cards for completing baseline, 13 and 17-week assessments. Incentive payments not only significantly improve recruitment rates[229], but there are no significant differences in key dependent variables for those offered versus those not offered an incentive.[230] Provision of incentives equivalent to the demands of participation is vital to successfully recruiting minorities into research and getting a culturally representative diverse sample.[231-234] After every assessment, participants will receive thank you letters and gift cards from a large retail merchant in graduated amounts ($40 after 1st, $50 after 2nd and $60 after 3rd). The total compensation will be $150 for about 6-10 hours of participants' time over 17 weeks.

Strategies to minimize attrition. 1) Recruiters will emphasize the importance of participating in the entire intervention each week. 2) Survivors and caregivers will be asked to mark their calendars for study calls. 3) email or text reminders about upcoming telephone contacts will be sent if agreed to by participants. 4) Weekly calls will maintain contact with all participants for the entire study duration. 5) Graduated compensation for assessments will be provided. These strategies have worked well in the past. Participants will be assured of the confidentiality of all information and that refusing to participate will not alter their care. Survivors will continue to receive standard medical and nursing care and may seek care from their health providers for any health problems that arise. For dyads that refuse to participate, the recruiter will seek consent to collect their de-identified demographic data and ask about the reason for refusal. These data help us understand who declines and contribute to external validity and generalizability of the findings.

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.[31,210] Seven principles of language competence, cultural competence, ethical conduct, mission or purpose, empathy, graciousness and credibility[235] will be incorporated in all interactions. We will show cultural sensitivity along two dimensions.[236,237] 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*) inherent in our caregiver definition, which allowed survivors to choose the person to participate. [238] These techniques allow us to personalize our interactions, addressing both personal and cancer issues of concern. This approach is critical to gain trust (*confianza*).

Randomization. Following the baseline interview, dyads will be randomized to either SMSH alone (N=172 post-attrition) or to TIP-C+SMSH (N=60 post-attrition). A minimization algorithm will be programmed by Dr. Sikorskii to balance arms by recruitment location, site of cancer, stage of cancer (early versus late), type of treatment, and survivor's relationship to the caregiver (spouse vs non-spouse).[239] The second randomization will occur for those who do not respond to the SMSH alone after the first 4 weeks using the same approach as the first randomization except in 1:1 ratio. The study coordinator will run the computer algorithm from the main study office (Tucson) to ensure allocation, concealment, and blinding.

5.0 RESEARCH DESIGN, METHODS AND PROCEDURES

Describe research design, methods and all study procedures

We will use two evidence-based interventions extensively tested against active and passive controls in traditional randomized controlled trials (RCTs). While overall efficacy of these interventions has been established[7,15,16,29-31], individuals differ in their responses. When an intervention does not initially work, clinical logic is to either extend the timeframe or prescribe a different intervention. Yet, these alternatives are seldom tested and not evidence-based. The proposed project advances beyond a traditional RCT of testing fixed "one size fits all" interventions to the sequential multiple assignment randomized trial (SMART) [32-37] design to build the evidence base for intervention sequencing that accounts for heterogeneity of responses. The first intervention, a printed Symptom Management and Survivorship Handbook (SMSH) with strategies for self-management of symptoms common during chemotherapy[15,16,30] will be given to both survivor and caregiver (the dyad). SMSH strategies, if successfully enacted by the dyad, produce positive symptom responses for the survivor. However, psychological distress of the survivor or the caregiver may diminish the receipt and enactment of the SMSH strategies and also exacerbate the severity of other symptoms[38] which, in turn, produces poor symptom responses.[39] Research by this team[40,41] and others[42-48] has documented dyadic effects where survivors' psychosocial distress impacts that of the caregiver and vice versa.[49] The survivor's and caregiver's distress exhibit similar trajectories. Therefore, the second intervention tested in sequencing is the 8-week telephone interpersonal counseling intervention (TIP-C) to manage psychological distress of the dyad.[8,50] This project will determine which dyads require which intervention sequence: SMSH alone, SMSH alone stepped up with TIP-C based on demonstrated needs after giving SMSH alone 4 weeks of time, or a combined TIP-C+SMSH for the first 8 weeks then SMSH alone for 4 weeks. Dyads will be initially randomized to either SMSH alone or TIP-C+SMSH (Figure 1). If the survivor's depression or anxiety does not respond to SMSH alone at week 4, dyads will be re-randomized to the TIPC+ SMSH or continue with SMSH alone. Outcome data will be collected at baseline, weeks 13 (post-intervention) and 17 (follow-up). Brief assessments during weeks 1-12 will track any change in the dyad's symptoms, intervention receipt, enactment and fidelity. Assessments and interventions are telephone-delivered in English or Spanish based on participant preference, as done in past studies.[8,50,51]

Design. We selected the SMART design (Figure 1) for this study over alternative designs (e.g., implementation designs) because the SMART design allows a precision or personalized approach to determine the right treatment at the right dose with the right sequence for the right survivor-caregiver dyad. SMART designs, although newer, show promise in developing the sequences of evidence-based interventions for more efficient and individualized patient- and caregiver-centered care. We will use findings from this study to create an algorithm for clinically meaningful decision making about symptom management for survivors and their caregivers to be tested in future implementation/dissemination studies. We will recruit 298 cancer survivors undergoing chemotherapy, targeted therapy, or hormonal therapy for a solid tumor at the NCI designated University of Arizona Comprehensive Cancer Center (UACC, Tucson and Phoenix locations) and at Arizona community oncology settings. The survivors will be screened for moderate or severe depression and/or anxiety prior to enrollment and identify the informal caregivers who will participate in the study. Following enrollment, informed consent and baseline interview of both survivor and caregiver, the dyad will be randomly assigned to either: 1) SMSH alone or 2) TIP-C+SMSH for 8 weeks followed by continued SMSH alone for
4 weeks. During 12 weeks following initial randomization, all participants will receive weekly telephone contacts to assess symptoms, deliver the assigned intervention and assess its enactment and fidelity. After the initial 4 weeks in the SMSH alone group, the survivor's response to the intervention will be determined. If the survivor responds (defined as a reduced score on depression and/or anxiety) (See C9a. Primary Outcomes), the dyad will continue with the SMSH alone for 8 more weeks. If the survivor is a non-responder (defined as no improvement or a worsening score for depression and/or anxiety), the dyad will be re-randomized to either continue with SMSH alone for 8 more weeks, or add 8 weeks of TIP-C. The rationale for using the survivor's response as the criterion for re-randomization is from the extensive evidence of interdependence in survivor and caregiver outcomes presented, and on the caregiver's focus on the survivor's outcomes. The rationale for timing of the assessment of response and re-randomization to add the TIP-C intervention after 4 weeks is based on past testing of the SMSH,[15,16,30] where median time to response on psychological distress ranged from 14 to 24 days. Post-intervention and follow-up telephone assessments are at weeks 13 and 17.

Analytic Methods

Data management. All data will be entered into the secure web-based database. Quarterly quality assurance checks of the data will be performed by the RA supervised by Dr. Sikorskii. De-identified data will be transferred into SAS 9.4 for analyses. The distributions of outcomes and potential covariates will be assessed, 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.

Attrition Analyses and Handling of Missing Data. We will compare dyadic characteristics of those who completed the study to those who did not within their designated group to inform the generalizability of findings. Attrition will also be compared between each pair of randomized groups. The regression techniques described below allow for missing at random (MAR) mechanism.[264] 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),[265,266] and sensitivity analyses will investigate the robustness of the results.

Primary Analysis. Primary analyses will follow the intent to treat approach.

Aim 1, Hypothesis 1: Dyads initially randomized to the TIP-C+SMSH will report lower depression, anxiety, and summed severity of other symptoms at weeks 1-12, 13, and 17, and lower unscheduled health services use, higher self-efficacy and social support, and lower caregiver burden at weeks 13 and 17 as compared to those initially randomized to the SMSH alone. This hypothesis will be tested using statistical model #1 that relates repeated measures of the survivor or caregiver outcome *y* (one at a time) to the group assignment variable $xx1$, outcome at baseline $xx2$, time entered as a class variable to model potentially non-linear patterns, and other covariates. For normally distributed outcomes, this model will be fit as a linear mixed effects model (LME). Generalized linear mixed effects (GLME) modeling will be used if outcome is not normally distributed and cannot be normalized using transformations. For health service use, statistical model #1 will be implemented as a GLME model with Poisson distributed errors, or as a zero-inflated Poisson or negative Binomial model based on the distribution of the counts of different health services uses. Each type of health services use (e.g., hospitalizations, ED visits) will be analyzed separately. The explanatory variables including study group will be evaluated as predictors of zero inflation (whether or not the count is zero), and also as predictors of the magnitude of the count when it is not zero. The main effects of the group variable $xx1$will be tested.

Aim 2, Hypothesis 2: Dyads where survivors do not respond to the SMSH alone during weeks 1-4 and have TIP-C added during weeks 5-12, will report lower depression, anxiety, and summed severity of other symptoms at weeks 5-12, 13, and 17, and lower unscheduled health services use, higher self-efficacy and social support, and lower caregiver burden at weeks 13 and 17 as compared to those who are re-randomized to continue with the SMSH alone. The strategy described under the analyses for Aim 1 will be implemented for the repeated outcome measures during weeks 5-12 and weeks 13 and 17 that will be related to group assignment from the second randomization, symptom severity during week 4, time, and covariates.

Mediation analyses for Aims 1 and 2. To test for mediation, the 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 symptom outcome variable at weeks 13 and 17, with the baseline measure of that respective symptom outcome variable treated as a covariate. Caregiver burden will be tested only at the individual level, but social support and self-efficacy will be tested at the individual and dyadic levels. We will use a bias corrected bootstrapping analytic strategy[267,268] based on 5000 bootstrap samples to estimate confidence intervals around the indirect effect of study group on the outcome variable, through the mediator. To establish mediation, the 95% confidence interval around the indirect effect must not include 0.

Aim 3 examines the dyadic interdependence in outcomes between survivors and caregivers. This interdependence will be modeled and tested with the actor-partner interdependence mediation model (APIMem)[269] in structural equation modeling. The APIMem estimates three classes of effects: actor effects (e.g., person A independent variable (IV)→person A dependent variable (DV)), caregiver (partner) effects (e.g., person A IV→person B DV), and mediation effects (e.g., person A IV→ person B Mediator→ person A DV) in an omnibus model. These models will specify correlations between the survivors' and caregivers' IVs as well as covariances between the error terms of the mediators and outcome variables, recognizing that these residuals will covary between dyad members due to unmeasured common causes. We will fit both a saturated version of the model in which all actor, partner, and mediation effects are free to vary and compare that with a

constrained model in which the effects for one dyad member are constrained equal to the corresponding effects of the other dyad member. The χ_2 difference test will determine whether the more parsimonious constrained model or the unconstrained model will be interpreted. This test will also indicate whether the effect for survivors is significantly different from that of caregivers. These models will test whether baseline to week 17 changes in survivors' outcomes of depression, anxiety and summed severity of other symptoms are mediated by the intervening (week 13) state or caregivers' outcomes or potential covariates.

Exploratory Aim 4. The dyadic 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 decision rule (dd_1, dd_2) specifying the first and second intervention to achieve optimal outcome will be using the Qlearning optimization method[258,270-272] implemented in SAS PROC QLEARN.[273 274] The Q-learning algorithm proceeds backwards from the last decision to the first. Two Q-functions will be considered. The function $QQ_2(HH_2) = EE[YY_2|HH_2]$ is the expectation of the second stage outcome YY_2 given history after 2 stages, denoted by HH_2: dyadic characteristics, outcomes observed during weeks 1-12, 13 and 17, and interventions received. The function $QQ_1(HH_1) = EE[YY_1 + \max QQ_2(HH_2)]$ uses history through the first intervention stage HH_1. The conditional expectations in the Q-functions will be estimated from regression analyses for the primary outcomes, and the optimal decision rules will be found using backward induction by maximizing these functions.[275,276] The product of this analysis will be identification of tailoring variables to operationalize the decision rules of selecting the optimal first intervention and switching from SMSH alone to TIP-C+SMSH. These personalized decision rules can then undergo testing in a future confirmatory RCT.

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.

Measures

Patient Reported Outcomes Measurement Information System (PROMIS) [249] measures are suitable for both survivors and caregivers, 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. The available short forms have evidence of good reliability and validity. [249] Our other measures also have good reliability (α > .80)[41,84,178,205] and validity, have been translated[240] and tested with Spanish speaking participants in our pilot studies.[31]

Primary outcomes.

Caregivers' and survivors' symptoms will be measured using the adapted General Symptom Distress Scale (GSDS),[124,250] a brief instrument that allows for a quick assessment of symptoms, which is especially important during weekly calls. It evaluates 15 symptoms: shortness of breath, nausea, vomiting, pain, sleep difficulties, bowel problems, numbness or tingling, skin rashes or sores, swelling in hands and feet, difficulty concentrating, poor appetite, cough, depression, anxiety, fatigue. Respondents indicate presence of each symptom (yes/no) and rate their severity on the scale from 1 to 10. The ability to manage symptoms is also assessed on a scale from 1=cannot manage to 10=can manage extremely well. The GSDS has good test-retest and internal consistency reliability and predictive and construct validity in both English and Spanish.[250] The 0-10 ratings of depression and anxiety and the summed severity of other 13 symptoms will be derived at each weekly contact, baseline, 13, and 17 week interviews.

Survivors' symptom response on depression and/or anxiety during weeks 1-4 as a criterion for rerandomization. Response will be assessed using the depression and anxiety items of the GSDS administered during weekly calls to survivors. Based on the inclusion criteria and established and validated symptom cut points, [224] survivors will enter with moderate or severe depression and/or anxiety (one symptom or both) . The cut-points are anchored in how much symptoms are distressing the participant by interfering with enjoyment of life, social relationships, and general daily activities. Participants indicate the severity/distress from 1 to 10. For depression, the mild category corresponds to a severity score of 1, the moderate category corresponds to scores 2-3, and scores of 4-10 fall into the severe category. For anxiety, the mild category is

severity of 1-3, the moderate category corresponds to scores 4-5, and the severe category is 6-10. Survivors who start at severe or moderate on depression and/or anxiety symptoms at intake and end at a lower category by the week 4 observation will be called **responders to the intervention**.[228] If a symptom was mild at intake, symptom response would not be applicable. Because responders demonstrate substantial improvement anchored to symptom distress after 4 weeks, responders will continue with the SMSH only intervention for another 8 weeks. **Non-responders to the intervention** are survivors who do not respond on either or both symptoms.[224,251,252] Non-responding survivors and their caregivers will be re-randomized to either continue with the SMSH alone for 8 weeks to give it additional time or add TIP-C for 8 weeks to rigorously test the value added by the more intensive intervention in Aim 2. Total intervention time is 12 weeks.

Caregivers' and survivors' depression and anxiety. PROMIS-short forms 8: depression and anxiety[253-256] will be administered at baseline, 13 and 17 week telephone interviews to provide greater detail and precision in the measurement of these outcomes, as compared to single GSDS items administered in weekly calls. We chose 8-item short forms to minimize respondent burden while maintaining measurement precision.

Secondary outcomes. Secondary outcomes are caregivers' and survivors' hospitalizations, urgent care or ED visits during the study. In baseline, week 13 and 17 interviews over the telephone, each dyad member will be asked to recall ED visits and admissions to hospitals and, if they occurred, their reasons and duration. Recall period will be 3 months in baseline and week 13, and 1 month in week 17 interviews. Extensive previous research[2-5] documents self-report is a reliable and valid method to collect health services use data especially when standardized methods are used and the recall period is short, as in this project. Self-report is the only reasonable and cost-effective way to assess healthcare use, as it would be impossible to access health (medical) records across the multiple systems and payers used by participants in this study.

Potential mediators.

Caregivers' and survivors' self-efficacy. PROMIS 4-item short forms (sf) will be administered in interviews.[253-256] Self-efficacy specific to symptom management will be captured by the GSDS item described above.

Caregivers' and survivors' social support. PROMIS 4-item-sf for emotional support and PROMIS Informational Support 4a will be used in interviews.[253-256]

Caregiver Reaction Assessment Tool.[257] This caregiver burden tool was developed and validated with caregivers of patients with chronic conditions. It has 5 subscales: impact on schedule, caregiver's esteem, family support, impact on health, and impact on finances, with Cronbach's alphas exceeding 0.70.

Potential Covariates and Future Tailoring Variables. These variables will be assessed during baseline interviews of survivors and caregivers. Demographic characteristics include caregivers' and survivors' age, education, work, ethnicity, race, acculturation, marital status, relationship between survivor and the caregiver, and living arrangement. Comorbidity will be measured with the Bayliss tool that queries the presence of 20 comorbidities,[258] and we will also collect height and weight to calculate BMI. The validity and reliability of self-reported height and weight are adequate[259-261], and health risk estimates associated with BMI values are virtually the same, whether based on self-report or measured BMI values.[262] Caregiver's activities of survivor care will be measured using a checklist[19], and quality of relationship will be measured using a 6-item index designed to assess the relationship quality. The index has established reliability with samples of married couples[263] and has also been used to capture survivors' perceptions of the quality of relationship with their friend/family caregiver. Preferred language of intervention delivery will be tracked. Receipt and enactment of intervention strategies are measured during weeks 1-12. Receipt will be measured by the number of completed weekly sessions. Enactment of the SMSH strategies is assessed at the beginning of calls during weeks 2-12 as described in section C8c. 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. Assessment of survivors' radiation, surgery, chemotherapy, targeted or hormonal therapy (dose, type, dates received), cancer site and stage, and medications (e.g., supportive agents for symptoms) will be collected from health record data corresponding with the time-on-study. Every effort has been made to keep respondent burden to a minimum and to distribute any burden over the course of the study. If needed, we can divide the assessments into two sessions over two days. Yet, few participants requested such accommodations in past studies.

7.0 DETAILED DESCRIPTION OF INTERVENTION

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

Interventions. We deliver interventions via the telephone (see section C2e for rationale) at convenient times for both the survivor and caregiver, including evenings and weekends.
Symptom Management and Survivorship Handbook (SMSM). is an evidence-based self-care management guide specific to each symptom.[84-87] Each module is presented in 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 oncology practice; other resources for management are listed. The previously tested English version will be translated into Spanish using an adaptation of Brislin's translation/back translation process[240] used by this team in the past. Professor Jaime Fatás-Cabeza, Director of the Undergraduate Translation and Interpretation Program at the University of Arizona, will oversee the translation. Cultural experts will perform back translations of a random sample of pages from the SMSH for comparison to the original English language versions, and all discrepancies corrected between the back translated and original English language pages. Finally, a focus group of six Spanish-speaking Latinos will discuss the translation in terms of understandability (language level and complexity), use of idioms, and consistency of meaning. Focus group data will be used to finalize the SMSH translation and layout (i.e. design).
Survivors and caregivers will be mailed the Handbook in the participant's preferred language following the baseline interviews. During each week, staff will call the survivors and then their caregivers. The call will begin with the assessment of symptoms using the General Symptom Distress Scale (GSDS, described in measures). 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 management[83] and used successfully in past work.[75,76,81,82,89] During weeks 2-12, the survivor's calls will begin with assessing SMSH use since the last call (intervention enactment), followed by the administration of the GSDS and referral to the SMSH. During weekly calls to caregivers, symptoms will also be assessed using GSDS. The caregivers will be notified of any current symptoms above threshold experienced by survivors and directed to the SMSH to assist the survivors in intervention enactment. Sharing symptom information between survivor and caregiver will be part of the informed consent. During weeks 2-12, the caregiver's calls will begin with assessing SMSH use for the management of survivors' symptoms, followed by the GSDS, summary of survivors' symptoms and referral to the SMSH. Calls will last about 10 minutes.

Table 2: TIP-C Intervention for Survivors and Informal Caregivers

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 informal caregiver (IC) and health care providers (HCP).
3	Role transitions, effective social skills for coping/adapting to cancer, role playing interpersonal interactions: IC & HCP, accessing resources
4	Role disputes/role transitions, focus on communication with IC & 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 with the IC.
7	Progress with cancer treatment. 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).

Telephone Interpersonal Counseling Intervention (TIP-C). Social work counselors with a master's degree and behavioral health and oncology expertise will deliver the 8-week TIP-C intervention (Table 2).

During weekly contacts, the counselors target 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. Counselors 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 survivorship care recommendations[241] and recent evidence showing that improved psychological well-being occurs when an intervention addresses practical resource needs.[242]

Each survivor and caregiver receiving the TIP-C+SMSH intervention will receive one 40-minute telephone call per week for 8 weeks (8 sessions). The first 10 minutes of the call will follow the SMSH only intervention procedures (see C8c). The next 30 minutes will be devoted to the delivery of TIP-C. The TIP-C sessions will incorporate the symptoms assessment performed at the beginning of the call as follows: discussion of depression, anxiety and stress per protocol and referral to the SMSH for symptoms. The final 4 weeks will be SMSH only. The TIP-C intervention protocol is the same for both survivor and caregiver, the same counselor will be assigned to both members of the dyad and sessions conducted in either Spanish or English.

Counselors call the survivor and caregiver at separate convenient times to ensure they have adequate time and privacy to participate. Numerous interventions for cancer survivorship use individually delivered methods [243-245] as we will use in this study. Dyadic delivery (i.e., both present at the same time) is not required and separate delivery resolves two major obstacles associated with delivering TIP-C to both members simultaneously. 1) Participants may be unwilling to discuss certain issues when the other dyad member is present such as discussing concerns that they have about each other. In such cases, the counselor can be an effective bridge between the two. Other times, participants may wish to discuss personal concerns (e.g., survivor dying). 2) Scheduling and technological difficulties multiply when both members must speak on the phone with a third party at the same time.

Training and intervention fidelity. Intervention protocol fidelity will be assured using established methods outlined by the NIH Treatment Fidelity Workgroup on consistency in dose, providers, delivery, and receipt of the intervention.[246] TIP-C interveners 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 from previous studies.[41,205,209,247] Counselors will listen to 8-10 hours of counseling sessions recorded for training purposes. Drs. Badger and Segrin will conduct training that will continue until the counselor is rated as achieving > 90% on protocol implementation. Annual re-training occurs throughout the study.

The intervention fidelity protocols used in past studies will be used in this study. All sessions will be 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).[142,153,206] 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. No one with less than 90% adherence will receive 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 after a second retraining will be replaced.

Intervention reproducibility. Interventions must be standardized, yet the complexities of symptom distress demand a flexible approach to preserve the relevance of TIP-C for the individual. We will determine the amount of elements personalized to the specific needs of the individual 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.[248] Participants who miss sessions (occurrence is rare) will be rescheduled, 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 also send an e-mail, text, or letter asking the participant to call us. Attrition rates and reasons will be documented, including being unable to reach the survivor or the caregiver or expressed desire to discontinue.

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. These variables will be assessed during baseline interviews of survivors and caregivers. Demographic characteristics include caregivers' and survivors' age, education, work, ethnicity, race, acculturation, marital status, relationship between survivor and the caregiver, and living arrangement. Comorbidity will be measured with the Bayliss tool that queries the presence of 20 comorbidities,[258] and we will also collect height and weight to calculate BMI. The validity and reliability of self-reported height and weight are adequate[259-261], and health risk estimates associated with BMI values are virtually the same, whether based on self-report or measured BMI values.[262] Caregiver's activities of survivor care will be measured using a checklist[19], and quality of relationship will be measured using a 6-item index designed to assess the relationship quality. The index has established reliability with samples of married couples[263] and has also been used to capture survivors' perceptions of the quality of relationship with their friend/family caregiver. Preferred language of intervention delivery will be tracked. Receipt and enactment of intervention strategies are measured during weeks 1-12. Receipt will be measured by the number of completed weekly sessions. Enactment of the SMSH strategies is assessed at the beginning of calls during weeks 2-12 as described in section C8c. 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. Assessment of survivors' radiation, surgery, chemotherapy, targeted or hormonal therapy (dose, type, dates received), cancer site and stage, and medications (e.g., supportive agents for symptoms) will be collected from health record data corresponding with the time-on-study. Every effort has been made to keep respondent burden to a minimum and to distribute any burden over the course of the study. If needed, we can divide the assessments into two sessions over two days. Yet, few participants requested such accommodations in past studies.

Scientific Rigor and Transparency. The scientific rigor of this study is ensured by the randomized design, complete inclusion/exclusion criteria defining the population to which findings would be generalizable, 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, transparent assessment and statistical analysis plans including attention to biases and the missing data.

Sex as a biological variable. We will consider survivors' and caregivers' sex as covariates in all analyses. Past research indicates that the survivor-caregiver relationship (spouse/partner versus other) is a key factor that may influence outcomes[62,165] for the dyad over and above sex. Relationship will be controlled in randomization and considered along with sex as a covariate and potential future tailoring variable.

Analytic Methods

Data management. All data will be entered into the secure web-based database. Quarterly quality assurance checks of the data will be performed by the RA supervised by Dr. Sikorskii. De-identified data will be transferred into SAS 9.4 for analyses. The distributions of outcomes and potential covariates will be assessed, 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.

Attrition Analyses and Handling of Missing Data. We will compare dyadic characteristics of those who completed the study to those who did not within their designated group to inform the generalizability of findings. Attrition will also be compared between each pair of randomized groups. The regression techniques described below allow for missing at random (MAR) mechanism.[264] 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),[265,266] and sensitivity analyses will investigate the robustness of the results.

Primary Analysis. Primary analyses will follow the intent to treat approach.

Aim 1, Hypothesis 1: Dyads initially randomized to the TIP-C+SMSH will report lower depression, anxiety, and
summed severity of other symptoms at weeks 1-12, 13, and 17, and lower unscheduled health services use, higher self-efficacy and social support, and lower caregiver burden at weeks 13 and 17 as compared to those initially randomized to the SMSH alone. This hypothesis will be tested using statistical model #1 that relates repeated measures of the survivor or caregiver outcome *y* (one at a time) to the group assignment variable xx_1, outcome at baseline xx_2, time entered as a class variable to model potentially non-linear patterns, and other covariates. For normally distributed outcomes, this model will be fit as a linear mixed effects model (LME). Generalized linear mixed effects (GLME) modeling will be used if outcome is not normally distributed and cannot be normalized using transformations. For health service use, statistical model #1 will be implemented as a GLME model with Poisson distributed errors, or as a zero-inflated Poisson or negative Binomial model based on the distribution of the counts of different health services uses. Each type of health services use (e.g., hospitalizations, ED visits) will be analyzed separately. The explanatory variables including study group will be evaluated as predictors of zero inflation (whether or not the count is zero), and also as predictors of the magnitude of the count when it is not zero. The main effects of the group variable xx_1will be tested.

Aim 2, Hypothesis 2: Dyads where survivors do not respond to the SMSH alone during weeks 1-4 and have TIP-C added during weeks 5-12, will report lower depression, anxiety, and summed severity of other symptoms at weeks 5-12, 13, and 17, and lower unscheduled health services use, higher self-efficacy and social support, and lower caregiver burden at weeks 13 and 17 as compared to those who are re-randomized to continue with the SMSH alone. The strategy described under the analyses for Aim 1 will be implemented for the repeated outcome measures during weeks 5-12 and weeks 13 and 17 that will be related to group assignment from the second randomization, symptom severity during week 4, time, and covariates.

Mediation analyses for Aims 1 and 2. To test for mediation, the 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 symptom outcome variable at weeks 13 and 17, with the baseline measure of that respective symptom outcome variable treated as a covariate. Caregiver burden will be tested only at the individual level, but social support and self-efficacy will be tested at the individual and dyadic levels. We will use a bias corrected bootstrapping analytic strategy[267,268] based on 5000 bootstrap samples to estimate confidence intervals around the indirect effect of study group on the outcome variable, through the mediator. To establish mediation, the 95% confidence interval around the indirect effect must not include 0.

Aim 3 examines the dyadic interdependence in outcomes between survivors and caregivers. This interdependence will be modeled and tested with the actor-partner interdependence mediation model (APIMem)[269] in structural equation modeling. The APIMem estimates three classes of effects: actor effects (e.g., person A independent variable (IV)→person A dependent variable (DV)), caregiver (partner) effects (e.g., person A IV→person B DV), and mediation effects (e.g., person A IV→ person B Mediator→ person A DV) in an omnibus model. These models will specify correlations between the survivors' and caregivers' IVs as well as covariances between the error terms of the mediators and outcome variables, recognizing that these residuals will covary between dyad members due to unmeasured common causes. We will fit both a saturated version of the model in which all actor, partner, and mediation effects are free to vary and compare that with a constrained model in which the effects for one dyad member are constrained equal to the corresponding effects of the other dyad member. The χ_2 difference test will determine whether the more parsimonious constrained model or the unconstrained model will be interpreted. This test will also indicate whether the effect for survivors is significantly different from that of caregivers. These models will test whether baseline to week 17 changes in survivors' outcomes of depression, anxiety and summed severity of other symptoms are mediated by the intervening (week 13) state or caregivers' outcomes or potential covariates.

Exploratory Aim 4. The dyadic 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 decision rule (dd_1, dd_2) specifying the first and second intervention to achieve optimal outcome will be using the Qlearning optimization method[258,270-272] implemented in SAS PROC QLEARN.[273 274] The Q-learning algorithm proceeds backwards from the last decision to the first. Two Q-functions will be considered. The function $QQ_2(HH_2) = EE[YY_2|HH_2]$ is the expectation of the second stage outcome YY_2 given history after 2 stages, denoted by HH_2: dyadic characteristics, outcomes observed during weeks 1-12, 13 and 17, and interventions received. The function $QQ_1(HH_1) = EE[YY_1 + \max QQ_2(HH_2)]$ uses history through the first intervention stage HH_1. The conditional expectations in the Q-functions will be estimated from regression analyses for the primary outcomes, and the optimal decision rules will be found using backward induction by maximizing these functions.[275,276] The product of this analysis will be identification of tailoring variables to operationalize the decision rules of selecting the optimal first intervention and switching from SMSH alone to TIP-C+SMSH. These personalized decision rules can then undergo testing in a future confirmatory RCT.

Potential Difficulties/Limitations and Alternative Approaches

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 will be minimized by implementing protocols to maintain intervention fidelity. There are no high-risk aspects of this trial, and all procedures are non-invasive. We recognize that in addressing depression and anxiety our efforts might inadvertently produce detrimental psychological responses. Should this occur, our experienced interventionists will refer the survivor and/or caregiver 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 possible confounding preintervention influences. Three primary outcomes (depression, anxiety, and summed severity of other symptoms) and all hypotheses are stated a priori. In the exploratory analyses, the Benjamini-Hochberg or Hochberg adjustment[277-279] will be used to control the false discovery rate.

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 3 represents the timeline of the project over the 4 years. Table 4 represents the specific schedule of events for the project.

Table 3: 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, update manuals, hire/train staff	X	X														
Enroll subjects; deliver intervention; collect			X	X	X	X	X	X	X	X	X	X	X	X		
Complete survivor health 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

Table 4	IRB #: 1804501501	PI: Terry Badger, PhD				
Schedule Of Events: Improving Informal Caregivers' and Cancer Survivors' Psychological Dis						
Study Item, Service, or Activity NOTES:		Timepoint NOTES:				
Study Item, Service, or Activity	Screening	Baseline (wk 0)	Weeks 2-4	Weeks 2-12	Follow-up (wk 13)	Follow- up (wk 17)
Inclusion / Exclusion Criteria	X					
Consent and PHI Auth Signed	X					
Enroll participant, enter into the queue for baseline via telephone		X				
Telephone participant to do the baseline or reschedule based on their preference		X				
Randomize participant post baseline into SMSH or SMSH+ TIP-C Intervention		X				
Mail study welcome letter, Symptom Management Handbook		X				
Intervention delivery via telephone			X			
Rerandomized if survivor is not responding (SMSH only)			X			
Intervention delivery via telephone (those initially randomized to TIP-C stop TIP-C at week 8; continue with SMSH)				X		
Follow-up assessment via telephone					X	X
Follow-up assessment via telephone						
Satisfaction and Debriefing via telephone						X
Participant is mailed a thank you letter and gift card to thank them for their time		X				X

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 + SMSH 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.*
Recruiters- 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.

<u>Averse events and serious adverse events</u> 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 and Survivorship Handbook
- Weekly GSDS script
- Handbook form (internal document)
- TIP-C form (internal document)