

Examples of Funded Grants in Healthcare Delivery Research

Overview

The National Cancer Institute (NCI) frequently receives requests for examples of funded grant applications. Several investigators and their organizations agreed to let the Healthcare Delivery Research Program (HDRP) post excerpts of their healthcare delivery research grant applications online.

About

We are grateful to the investigators and their institutions for allowing us to provide this important resource to the community. We only include a copy of the SF 424 R&R Face Page, Project Summary/Abstract (Description), Project Narrative, Specific Aims, and Research Strategy; we do not include other SF 424 (R&R) forms or requisite information found in the full grant application (e.g., performance sites, key personnel, biographical sketches). To maintain confidentiality, we have redacted some information from these documents (e.g., budgets, social security numbers, home addresses, introduction to revised application).

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SF 424 R&R Face Page

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Grant Number: 1 R01 CA224282-01A1

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

FOA: PAR16-317

FOA Title: INTERVENING WITH CANCER CAREGIVERS TO IMPROVE PATIENT HEALTH OUTCOMES AND OPTIMIZE HEALTH CARE UTILIZATION (R01)

Organization: UNIVERSITY OF ARIZONA

Senior/Key Personnel: TERRY BADGER Ph.D

Organization: UNIVERSITY OF ARIZONA

Role Category: PD/PI

Project Summary/Abstract

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 Toolkit (SMT) 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 SMT alone or TIP-C +SMT. If the survivor's elevated depression or anxiety does not respond to SMT alone by week 4, dyads will be re-randomized to continue with SMT to give it more time or to TIP-C+SMT. 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+SMT as compared to the SMT 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) during 17 weeks (secondary outcomes); c) greater self-efficacy, social support, and lower caregiver burden during weeks 13 and 17 (potential mediators). **2)** Among non-responders to the SMT alone after 4 weeks, determine if dyads assigned to TIP-C+SMT as compared to the SMT 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 SMT 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.

Project Narrative

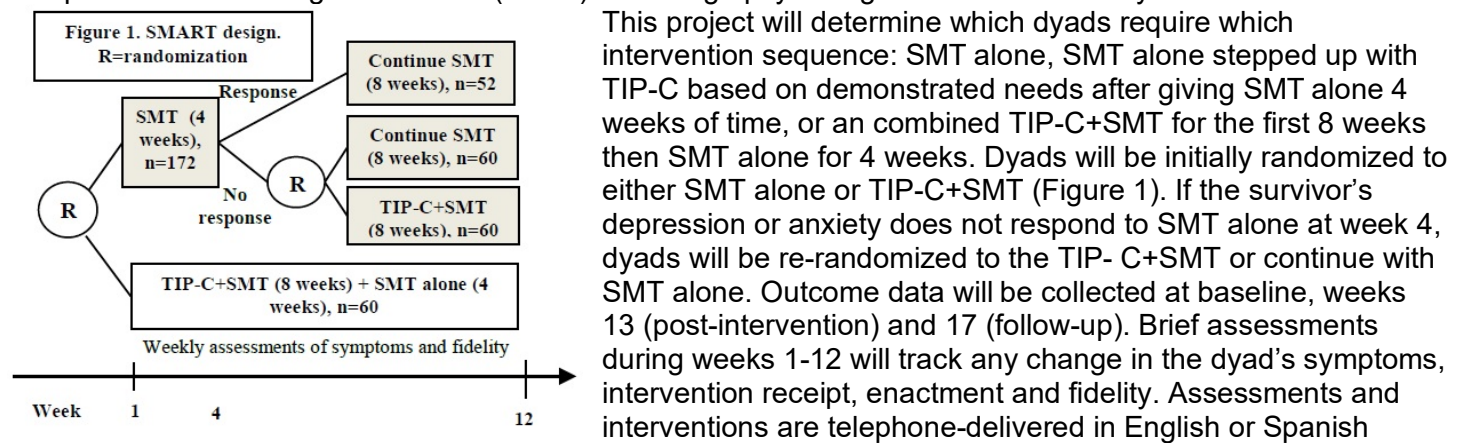
The proposed research will deliver two interventions (Telephone Interpersonal Counseling, Symptom Management Toolkit) and test their optimal sequencing to improve symptom management among 298 survivors' with known levels of distress and symptom severity and their 298 caregivers. We believe that by intervening with both the survivor and caregiver we can improve symptom management, increase self-efficacy, reduce health care use and decrease distress in both members of the survivor-caregiver dyad.

Specific Aims

Informal caregivers, typically family members or friends, provide more than half of the care needed for the 5.7 million cancer survivors (defined as individuals from diagnosis to end-of-life¹⁸) in the United States, often with negative consequences to their health.^{12,19-21} Caregivers assist with the management of the survivor's symptoms such as fatigue²², pain and insomnia,²³ and others.^{22,24-27} Psychological distress (depression and anxiety) has been reported in at least 30% of survivors²⁸ and their caregivers,^{8,19} who are not always prepared for the task of symptom management. This research assists both the caregiver and survivor (the dyad in this study) to manage the survivor's cancer- and treatment-related symptoms and the distress of both members of the dyad in a sample of 298 survivors with elevated depression or anxiety and their 298 caregivers. Dyads will be recruited during the survivor's chemotherapy or targeted therapy for a solid tumor, a time when symptom burden and psychological distress are particularly high.

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 toolkit (SMT) with strategies for self-management of symptoms common during chemotherapy^{15,16,30} will be given to both survivor and caregiver (the dyad). SMT 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 SMT strategies and also exacerbate the severity of other symptoms³⁸ which, in turn, produces poor symptom responses.³⁹ Research by this team^{40,41} and others⁴²⁻⁴⁸ 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: SMT alone, SMT alone stepped up with TIP-C based on demonstrated needs after giving SMT alone 4 weeks of time, or a combined TIP-C+SMT for the first 8 weeks then SMT alone for 4 weeks. Dyads will be initially randomized to either SMT alone or TIP-C+SMT (Figure 1). If the survivor's depression or anxiety does not respond to SMT alone at week 4, dyads will be re-randomized to the TIP-C+SMT or continue with SMT 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} Formal hypotheses are in the analysis section (C12) to direct testing of the following **specific aims**:

1. Determine if dyads in the TIP-C+SMT as compared to the SMT 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) during 17 weeks (secondary outcomes); c) greater self-efficacy, social support, and lower caregiver burden during weeks 13 and 17 (potential mediators).
2. Among non-responders to the SMT alone after 4 weeks, determine if dyads in TIP-C+SMT as compared to the SMT 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 survivors' and caregivers' primary and secondary outcomes.
4. Determine which characteristics of the dyad are associated with responses to the SMT 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 in the future.

The SMART design provides a state of the art framework for rigorous testing of intervention sequences and for developing decision rules for personalized symptom management for future implementation studies. Findings from this study can be used to improve symptom management in cancer survivors and caregivers.

A. Background and Significance

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 States⁵³ 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 activities⁵⁷ 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 SMT 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 (SMT) 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 burden¹⁰⁵⁻¹¹² 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.

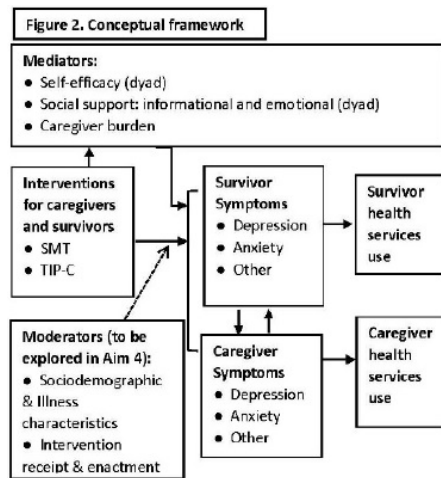
A series of longitudinal studies¹³⁰⁻¹³³ including those conducted by this team^{130,131}, found an association between increasing symptom prevalence and poorer physical and emotional functioning. Our team's past work¹³⁴ and that of others¹³⁵ documented the associations between reductions in symptoms 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.

Interventions sequenced in the proposed research. The Symptom Management Toolkit (SMT) is an evidence-based self-care management guide. The printed SMT 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} Research staff assess symptoms during the weekly telephone calls and refer survivors to the

specific SMT sections for elevated symptoms. In past studies, survivors were satisfied with this intervention and reported decreased symptom burden and improved psychosocial status.¹³⁶

Telephone Interpersonal Counseling Intervention (TIP-C). The TIP-C intervention is based on interpersonal psychotherapy. Social workers (called counselors) deliver the TIP-C intervention via weekly calls and use interpersonal communication techniques to focus on depression, anxiety, and interactions between the participant 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 studies¹³⁷⁻¹⁴¹ Other symptoms (e.g., fatigue, pain) decreased with TIP-C as well,¹⁴² which is consistent with the literature documenting the co-occurrence of depression with other symptoms.¹⁴³⁻¹⁴⁶ When depression is treated, other symptoms improve, leading to decreased health services use because symptoms are the primary driver of health care services use, including hospitalizations.^{9,10}

Conceptual framework. This study is informed by the NIH Symptom Science Model.¹⁴⁷ In our adaptation



(Figure 2), psychological symptoms (depression and anxiety) and other symptoms (e.g., fatigue, insomnia, pain) experienced by the survivor and caregiver have negative consequences on health and health care utilization.¹³⁴ The proposed interventions will alleviate the symptom burden for both dyad members through several key mediating variables, as tested in Aims 1 and 2. Symptom improvement occurs in part by mobilizing social support, increasing self-efficacy to perform tasks (e.g., symptom management) needed during cancer care.^{70,88,148,149} Both TIP-C and SMT target and improve self-efficacy and social support.¹⁵⁰ When caregivers participate in expansive social networks, a key target of the TIP-C intervention, caregiver burden decreases.⁸³ Based on this evidence, we will test survivors' self-efficacy and social support as mediators for intervention effects on survivors' symptoms, and caregivers' self-efficacy, social support, and burden as mediators for caregivers' symptom outcomes. Further, a substantial body of evidence indicates that the emotional and even physical well-being among survivors and their caregivers are

interdependent.^{12,41,77,87,151-154} Our own prior research with breast and prostate cancer survivors and their caregivers has documented dyadic interdependence on depression, negative affect, stress, anxiety, and fatigue.^{151-153,155} Caregivers' physical well-being is positively predictive of survivors' physical well-being^{66,156} and negatively predictive of survivors' psychological distress (depression and anxiety).^{149,157} Higher quality social support from caregivers is associated with lower cortisol concentrations and healthier neuro-endocrine functioning in survivors¹⁵⁸ and less negative consequences to physical and emotional health. When a caregiver meets the criteria for any psychiatric diagnosis, the survivor is 7.9 times more likely to have a psychiatric diagnosis of his or her own.⁶⁹ Depressed mood in a caregiver is associated with a 4.27 times higher risk of depressed mood in a cancer survivor.¹⁵⁹ This effect was not replicated in matched control dyads without cancer,¹¹ further suggesting that elements unique to cancer treatment and adjustment may be contributing to this dyadic interdependence. This interdependence will be tested in Aim 3 of this study; in addition, premised on this interdependence, for the first time we will test whether social support or self-efficacy of one member of the dyad mediate intervention effects on symptoms of the other member of the dyad (see Innovation section, item 4). Finally, the mediated relationship of intervention on symptoms may be influenced by the extent of intervention receipt and enactment³⁸ and "context of care" variables¹⁶⁰ that include socio-demographic, disease and treatment characteristics,¹⁶⁰ comorbidities (e.g., Body Mass Index (BMI) (height and weight)).^{161,162} Being overweight or obese is a well-established risk factor for depression and vice versa.¹⁶² Our past work showed that BMI was positively associated with depression and stress,¹⁶³ leading us to include high BMI and other multiple prevalent comorbidities in the pool of "context of care" variables. These variables, along with intervention receipt and enactment, will be explored as potential tailoring factors used in formulating the decision rules for choosing optimal personalized intervention sequences for survivors and caregivers (Aim 4). For example, a dyad where the survivor has high comorbidity may need TIP-C+SMT from the beginning to optimize outcomes, while a dyad where the survivor has low comorbidity could start with SMT and add TIP-C only if no symptom response is achieved after 4 weeks. We will use the evidence obtained in the analysis to create and refine algorithms for optimal allocation of resources to achieve the best possible outcomes for the dyad using the least labor-intensive intervention. We will test these algorithms or protocols in a future

implementation trial.

Scientific premise. The sequencing of the TIP-C and SMT arises from four closely interrelated premises.

1. Intervening with both members of the dyad. Interventions focused solely on survivors care recipients may not be effective in improving caregivers' emotional health.¹⁶⁴ Researchers have examined the feasibility and efficacy of interventions to support caregivers of cancer patients,¹⁶⁴⁻¹⁶⁸ including cognitive-behavioral and interpersonal counseling^{8,128,164,169-179}; communication with providers,^{120,180} and caregiver self-care.¹⁷³ As argued above under the conceptual framework, caregiver and survivor outcomes are interdependent, and we will deliver TIP-C to both the survivor and the caregiver.

2. Managing caregiver distress leads to improved outcomes for the survivor. Down regulated well-being in caregivers may compromise their abilities to care for themselves and others, potentially worsening health outcomes of the care recipient and even shortening survival.^{29,62,181,182} Survivors whose informal caregivers had greater depressive symptoms reported poorer quality in the informal caregiver's care.⁴² Consequently, the welfare of a caregiver is not only an important clinical endpoint in its own right, but is also extraordinarily consequential to the well-being of a cancer survivor.

3. Managing distress leads to greater receipt and enactment of symptom management strategies and better symptom responses. Psychological distress may diminish both engagement and response to symptom management strategies as seen in past work of this team³⁹ and others^{17,183}, suggesting the need to manage distress first. Although the SMT includes strategies to manage depression and anxiety, it may be not be sufficient to produce symptom responses for some survivors. Which dyads require higher intensity TIP-C to manage distress will be empirically determined in this study. In past work we found that by reducing psychological distress, improvements occurred in other symptoms (e.g., fatigue, pain), and in social and spiritual well-being.¹⁴² Thus, we propose that psychological distress is an important target for intervention with broader benefits beyond depression and anxiety.

4. We have established evidence of efficacy of both TIP-C and SMT (see section C2) from traditional RCTs and are pursuing the next step of investigating their optimal sequencing to address heterogeneity of response using the SMART design.³²⁻³⁵ It is vital to know the dynamic sequencing of interventions based on participant responses to personalize and enhance symptom management beyond static interventions.^{1,184,185} Our approach builds sequences that may start with a simpler easily implementable intervention such as the SMT, and then at a decision point typical in clinical practice (4 weeks), symptom response is evaluated. If an intervention is successful, it is continued. If it is not, then we need the rules to decide whether to continue the intervention by giving it more time, or intensify by adding a second therapeutic. As in practice, some dyads may need both interventions, TIP-C and SMT. This research will formulate the decision rules for choosing interventions as well as best timing of initiating the second intervention, TIP-C.

B. Innovation

The key innovations that maximize the potential of the intervention sequences to improve caregivers' and survivors' outcomes are:

1. Integration of two potentially synergistic interventions, SMT and TIP-C. For the first time, the SMT will be integrated with the TIP-C to achieve outcomes that are better than a simple sum of the two because, as argued under scientific premise, managing psychological distress may: a) improve the receipt and enactment of the SMT strategies; and b) alleviate other symptoms associated with it.

2. Rigorous investigation of intervention sequencing. The innovative SMART design rigorously investigates sequencing of interventions based on their success with individuals. The second randomization isolates the effect of intensifying the intervention versus giving a simpler one more time.

3. Dynamic delivery model. The innovative dynamic delivery model, where intervention intensity is adjusted based on demonstrated needs, is ideally suited for the temporal nature of symptoms that presents challenges to symptom management science.^{9,186-190}

4. Cutting edge statistical methods to produce new decision rules. Aim 3 will be achieved by employing the Actor-Partner Interdependence Mediation model (APIMeM) to test dyadic mediation. APIMeM has recently proven to be an effective tool for modeling interdependence in dyads coping with cancer.¹⁹¹ The concept of an intervention having an indirect effect on a recipient through the enhanced well-being of a caregiver has never been tested prior to this study. The Aim 4 analysis uses Q-learning to determine optimal decision rules for choosing intervention sequences in the future, based on dyadic characteristics. The resulting new clinical decision rules and algorithms optimize the delivery of supportive care given individual dyadic profiles.

5. Expanding SMT intervention to Spanish-speaking cancer survivors and their caregivers. Given the growing Hispanic/Latino cancer population worldwide,¹⁹² effective interventions that can be delivered in Spanish could have national and international impact. Although we have tested the TIP-C with Spanish-speaking survivors and caregivers, the SMT has not been tested, but will be for the first time in this project.

C. Approach

C1. 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) SMT alone or 2) TIP-C+SMT for 8 weeks followed by continued SMT 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 SMT 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 SMT 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 SMT 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 SMT,^{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.

C2. Preliminary Studies: Justification and feasibility.

C2a. Ability to recruit and retain cancer survivor-caregiver dyads. We have successfully recruited dyads through UACC and community sites for our previous work^{6,50,150} and ongoing studies: *Support for Latinas with Breast Cancer & Their Intimate and Family Partners*, American Cancer Society RSG-12-120-01-CPPB, MPls: T. Badger and C. Segrin, co-I: A. Sikorskii, 2012-2018; *Using SMART Design to Improve Symptom Management Strategies among Cancer Patients*, R01 CA193706, MPls: A. Sikorskii and G. Wyatt, co-I: T. Badger, 2015-2019. Our sample sizes ranged from 49 to 248 dyads (N=98 to 496 individuals) and include cancer survivors with various solid tumors and their caregivers. Survivors and caregivers were of both genders and all ethnicities. Attrition rates across studies were $\leq 25\%$.

C2b. 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.⁶⁻⁸ Survivor-caregiver dyads were randomly assigned to either TIP-C or a comparison group in each study and completed a minimum of three assessments over time. TIP-C focuses on the psychological distress of, and the interpersonal interactions between, the cancer survivor and the caregiver. 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 study⁷ showed depressive symptoms decreased over time for dyads in all groups (TIP-C, AC, exercise), and women's anxiety decreased in TIP-C 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.¹⁹³ In the next two studies^{8,50,142} and in our ongoing study with

Table 1. Post-intervention least square (LS) means, standard errors (SE) and effects sizes (Cohen's d) for the differences between TIP-C and THE on survivor and caregiver outcomes.

Outcome	TIP-C LS Mean (SE)	THE LS Mean (SE)	d
Survivor symptom distress	5.12 (0.31)	5.87 (0.48)	0.44
Survivor mental fatigue	5.41 (0.67)	6.91 (0.96)	0.39
Survivor social well-being	67.00 (1.74)	56.12 (3.18)	1.04
Caregiver depression	7.82 (1.38)	11.62 (1.30)	0.40

Latina dyads (current N=248 dyads, final N=260 dyads) which will be completed in December 2017,¹⁹⁴ we found significant decreases over time in depression, anxiety, negative affect, symptom distress and higher social support for survivors and caregivers in both groups. TIP-C was superior to THE on the outcomes listed in Table 1. The effect

sizes in this table were used to power the proposed trial. The ongoing trial also assesses health services use, and the preliminary data indicate that the odds of subsequent survivor hospitalizations increase 1.32 times (95% CI: 1.05-1.67, p=.02) per one unit of increase in symptom distress (0-10 scale). These preliminary data provide evidence for the efficacy of TIP-C for managing psychological distress and for the influence of distress on hospitalizations.

C2c. Evidence for the efficacy of the SMT. Drs. Barbara and Charles Given, developers of the SMT, and Dr. Sikorskii have tested the SMT in 3 RCTs. Automated telephone symptom management (ATSM) using the SMT was not different from nurse-assisted symptom management (NASM), previously found efficacious against control¹⁹⁵ in a sample of N=437 survivors with solid tumors on summed symptom severity.¹⁶ The ATSM/SMT was superior to the NASM in response to symptoms.^{15,16} Both arms achieved clinically significant reductions in symptom severity over baseline. Over a 10-week period, hospitalizations reduced from 39% to 26% among 140 patients with lung cancer, from 39% to 19% among 234 breast, from 47% to 9% among 80 colon, and from 41% to 19% among other cancers. Similar reductions were noted in emergency room visits.^{196,197} In another trial, NASM was compared to SMT delivered by a non-nurse coach among 234 survivors undergoing chemotherapy for advanced solid tumor cancers and their caregivers. Each arm reduced survivor symptom severity with no differences between arms.¹⁹⁸ Caregivers with lower depressive symptoms were more likely (OR = 1.99, 95% CI = 1.45-2.76) to provide symptom management assistance; and assistance with greater number of symptoms was associated with worse caregiver depression (p<.01) and burden (impact on schedule, p<.01).¹⁶⁵ In a recently completed study with 272 survivors treated with oral oncolytic agents,¹⁹⁹ significant declines in symptom severity in the SMT+ oral agent reminders arm compared to AC were found post intervention (p<.01). These studies provide evidence of the efficacy of SMT for managing multiple symptoms. Findings also show that interventions focused solely on the survivor may not be effective for improving caregivers' emotional health. We will deliver the interventions to both survivor and caregiver in the proposed trial based on this evidence.

C2d. Evidence of interdependence in survivor and caregiver outcomes. We have found in our previous studies^{12,41,77,87,151-154} that there was significant dyadic interdependence over time on symptoms of depression, anxiety, negative affect, and symptom distress. Psychological distress of the survivor was predicted by caregivers' psychological distress, which was often equal to or higher than the survivor.¹⁵⁵ We found dyadic interdependence in physical symptoms (e.g., fatigue, pain, insomnia) as well.^{194,200} These findings further confirm the need to intervene with both members of the dyad, as proposed in this trial.

C2e. Telephone delivery of the interventions and data collection. In our initial studies, we used the telephone to deliver the interventions to remove the many access barriers that clearly impede intervention receipt. Barriers include geographic access (e.g., rural), transportation costs, stigma, technology-associated anxiety and costs associated with internet delivery methods. Nationally, 98% of individuals have telephone access²⁰¹ 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.²⁰² In our past work, intervention delivery via face-to-face, videophones, internet and interactive voice response systems was inferior to a live person on the telephone with respect to adherence and satisfaction. Consistent with findings of others²⁰³, 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.²⁰⁴ After careful consideration, we will use the telephone for intervention delivery and data collection to facilitate success and scientific rigor of this project.

C2f. 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 C6e) and beliefs about the importance of immediate and extended family and close friends in health outcomes.²⁰⁵ All study related materials and interactions will be available in English and in Spanish. In summary, we have 1) the ability to recruit and retain dyadic (survivor-caregiver)

samples similar to the sample proposed here, 2) established the efficacy of TIP-C and SMT, 3) documented the strong interdependence between survivor-caregiver outcomes; 4) documented the benefits of the telephone-delivered intervention and data collection, and 5) delivered our protocols in English and Spanish.

C3. Team. Drs. Badger and Segrin have worked together for 16 years, completed multiple RCTs, each advancing the evidence base for the management of psychosocial distress in prostate and breast cancer survivors and their caregivers^{7,142,169,206}, establishing the interdependence in health outcomes between survivors and caregivers^{29,151,155,207}, refining the TIP-C intervention^{208,209}, and testing the intervention with Spanish-speaking and English-speaking participants.^{31,142,210} Drs. Given and Sikorskii have worked together for 14 years, completed 4 large multi-site symptom management RCTs^{15,16,198,211}, each building on the former expanding knowledge with respect to how self-care strategies lower symptom severity, the mechanisms through which this occurs, refining the SMT intervention, and the costs associated with producing these responses¹⁹⁶. These researchers joined forces in early 2016 with Drs. Sikorskii and Badger collaborating on the ongoing SMART study testing integrative therapies and Drs. Badger, Segrin and Sikorskii collaborating on the ACS-funded study focused on Latina dyads. Dr. Crane has worked and published with the research team,^{212,213} has extensive experience with assessment of behaviors among cancer survivors,²¹⁴⁻²¹⁸ and serves as an advisor to the UACC Behavior Measurement and Interventions Shared Resource. Dr. Given, a professor at Michigan State University, has worked with both Drs. Sikorskii and Badger. He is the author of the SMT and has extensive experience in analysis of health utilization data.^{196,219-223} Dr. Wong is a medical oncologist at the UACC, Phoenix campus. She and Drs. Badger, Sikorskii, and Crane are members of the Cancer Prevention and Control (CPC) Program of the UACC.

C4. Sample. We will recruit 298 dyads (see C5 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. 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.

There is an ample pool of cancer survivors available to meet enrollment targets. Of the estimated 35,810 newly diagnosed cases of cancer²²⁷ 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.

C5. 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, 120 dyads from two groups created by the second randomization will be non-responders to the SMT alone. From past work, response rate to the SMT on depression and anxiety was approximately 30%,²²⁸ therefore 120 non-responders will be 70% of 172 randomized to the SMT alone in the first randomization. The comparison of these 172 to 60 dyads allocated to the TIP-C+SMT 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.

C6. Recruitment and retention of participants.

C6a. 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.

C6b. 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+SMT versus SMT alone to help manage symptoms, 12 weekly calls and three interviews, no cost to study participation, risks/benefits, and incentives.

C6c. Subject incentives. We will provide gift cards for completing baseline, 13 and 17 week assessments. Incentive payments not only significantly improve recruitment rates²²⁹, 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.

C6d. 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) e-mail 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.

C6e. 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 credibility²³⁵ 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*).

C7. Randomization. Following the baseline interview, dyads will be randomized to either SMT alone (N=172 post-attrition) or to TIP-C+SMT (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 SMT 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.

C8. 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.

C8a. Symptom Management Toolkit (SMT) 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 process²⁴⁰ 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 SMT 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 SMT translation and layout (i.e. design).

Survivors and caregivers will be mailed the toolkit 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 SMT 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} During weeks 2-12, the survivor's calls will begin with assessing SMT use since the last call (intervention enactment), followed by the administration of the GSDS and referral to the SMT. 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 SMT 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 SMT use for the management of survivors' symptoms, followed by the GSDS, summary of survivors' symptoms and referral to the SMT. 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).

C8b. 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 recommendations²⁴¹ 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+SMT 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 SMT 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 SMT for symptoms. The final 4 weeks will be SMT 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 methods²⁴³⁻²⁴⁵ 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.

C8c. 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 $\geq 90\%$ 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 insure that $\geq 90\%$ 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.

C8d. 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.

C9. 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 ($\alpha \geq .80$)^{41,84,178,205} and validity, have been translated²⁴⁰ and tested with Spanish speaking participants in our pilot studies.³¹ Measures are in Appendix A.

C9a. 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 re-randomization. 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 SMT 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 SMT 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 anxiety²⁵³⁻²⁵⁶ 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.

C9b. 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 research²⁻⁵ 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.

C9c. Potential mediators.

Caregivers' and survivors' self-efficacy. PROMIS 8-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 8-item-sf for instrumental and emotional support 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.

C9d. 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 adequate²⁵⁹⁻²⁶¹, 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 checklist¹⁹, 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 couples²⁶³ 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 SMT 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.

C10. 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.

C11. 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.

C12. Analytic Methods

C12a. 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.

C12c. 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.

C12e. Primary Analysis. Primary analyses will follow the intent to treat approach.

Aim 1, Hypothesis 1: Dyads initially randomized to the TIP-C+SMT 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 SMT 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 x_1 , outcome at baseline x_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 x_1 will be tested.

Aim 2, Hypothesis 2: Dyads where survivors do not respond to the SMT 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 SMT 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 (d_1, d_2) specifying the first and second intervention to achieve optimal outcome will be using the Q-learning 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 $Q_2(H_2) = E[V_2 | H_2]$ is the expectation of the second stage outcome V_2 given history after 2 stages, denoted by H_2 : dyadic characteristics, outcomes observed during weeks 1-12, 13 and 17, and interventions received. The function $Q_1(H_1) = E[V_1 + \max Q_2(H_2)]$ uses history through the first intervention stage H_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 SMT alone to TIP-C+SMT. These personalized decision rules can then undergo testing in a future confirmatory RCT.

C13. Potential Difficulties/Limitations and Alternative Approaches

Table 3 shows the project timeline. Potential problems from recruitment and retention will be minimized by the use of our previous methods yielding high retention rates with no differential attrition between conditions.

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	X		
Complete survivor health record audits				X	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	X

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 pre-intervention 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 adjustment²⁷⁷⁻²⁷⁹ will be used to control the false discovery rate.

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