Using SMART Design to Improve Symptom Management Strategies Among Cancer Patients

National Cancer Institute Grant # 1 R01 CA193706

Study Protocol and Statistical Plan

May 28, 2020

Research Strategy

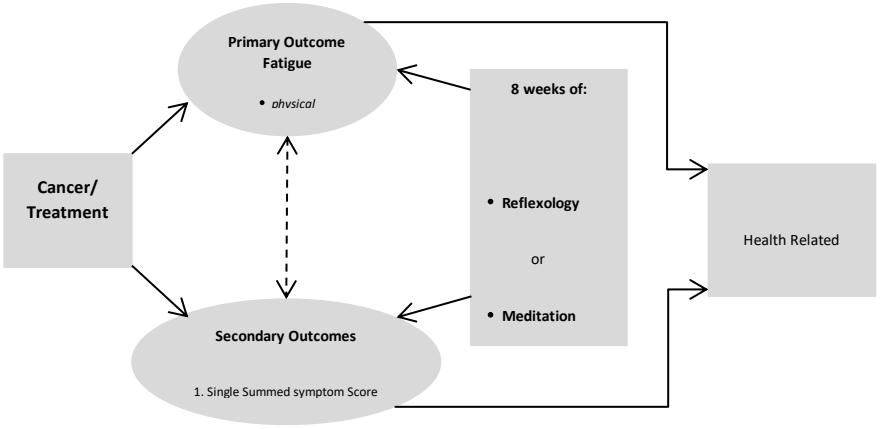
B. Significance

1. Symptoms during Treatment: Solid Tumor Cancer Patients. By 2030, cancer will surpass heart disease as the leading cause of death in the United States, with new cases expected to increase nearly 45% from 1.6 million to 2.3 million annually.[1] Of highest significance to clinical practice, these patients are likely to experience the burden of symptoms resulting from cancer and its treatment,[2-4] leading to diminished health related quality of life (HRQOL).[5-9] The adapted Barsevick symptom management model[10] (Figure 2) guides this study. Based on the model, improved symptom management, especially fatigue, is the proposed mechanism for improving HRQOL.

Symptoms are defined as patient's perceptions of abnormal emotional and physical states.[11]

Primary Outcome: Fatigue is the most prevalent and often distressing symptom related to cancer and its treatment.[12] The prevalence of cancer-related fatigue during active treatment ranges from 25% to 99% based on the sample and methods of assessment.[13] Cancer-related fatigue is the perception of unusual tiredness that varies in pattern and severity and has a negative impact on ability to function in people who have or have had cancer.[10] Due to the high prevalence of fatigue and this team's completed work showing efficacy of two interventions for this symptom,[5,14] fatigue is the primary outcome of the proposed study. Fatigue is known to affect HRQOL outcomes.[10,15-20] The biological changes due to chemotherapy and the resulting inflammatory processes may be responsible for the persistence of fatigue, as well as related symptoms.[21-23] Physical, emotional and cognitive components of fatigue will be captured in this study.

Figure 2: Adapted Symptom Management Model



Secondary Symptom Outcomes: In a survey of a 1000 cancer patients, the mean number of symptoms reported was eleven.[24] Therefore we will evaluate three secondary outcomes: 1) summed severity score across an array of symptoms other than fatigue (to avoid duplication with primary outcome) from the expanded M.D. Anderson Symptom Inventory (MDASI)[25,26] pain, nausea, disturbed sleep, distress, shortness of breath (dyspnea), difficulty remembering, decreased appetite, drowsiness, dry mouth, sadness, vomiting, numbness/tingling, cough, constipation, diarrhea, sore mouth, rash, and hair loss; 2) depressive symptoms; and 3) anxiety. A key symptom example from the MDASI is dyspnea, a multidimensional subjective experience of breathing distress that impairs functional status, and is associated with thoughts about

disability, lowered hopefulness, and existential problems in individuals with cancer.[27,28] In our completed studies with reflexology and meditative practices, there was a significant improvement in self-reported dyspnea.[5,29] We will also assess two symptoms not specifically included in MDASI: depression and anxiety that are common in cancer patients and are a source of high distress and decrease in HRQOL.[30,31] Our preliminary data,[32,33] published work,[5,14] and work of others[13,26-30] indicate the interventions we propose in this study may impact primarily fatigue, but also dyspnea, depression and anxiety.[14,26,34-37] One primary and three secondary outcomes evaluated in this study will reflect the burden of multiple symptoms that cancer patients experience.

2. Home-Based Symptom Management with Caregivers. This project is also significant because it meaningfully engages a friend or family member in their patients' supportive care over time. Many randomized controlled trials (RCT) of symptom management interventions, including complementary therapies, consist of an intervention period of several weeks, which does not cover the full duration of cancer treatment. Since symptom management is needed not just for a few weeks, but for the entire cancer treatment and beyond, the engagement of a friend or family caregiver may represent a significant solution to the sustainability of home-based symptom management interventions. In our nearly completed R01 with reflexology for cancer symptom management, we engage friend or family caregivers.[33] A friend or family caregiver is identified as such by the patient and provides unpaid assistance to a person with a chronic or disabling condition such as cancer.[38,39] Currently, the estimated number of cancer patient caregivers is 5.7 million people. The value of this unpaid labor force of caregivers in the U.S.[40,41] is appraised to be at least $306 billion annually.[42,43] It is recognized that the support provided by caregivers may influence the outcomes of their patient's cancer treatment.[38,44-46] Caregivers may also be an important influence on patient care options since they are key stakeholders in patients' symptom management. In this sense, interventions that support the patient may also indirectly support the caregiver.[47,48] For these reasons, our project targets the caregiver along with the patient to engage in the home-based symptom management intervention/s.

Home-based Interventions. Despite the high needs for symptom care, patients undergoing cancer treatment have limited choices, given their unique vulnerabilities.[49] Reduced functional status can lead to difficulties with the use of supportive therapies that require travel or a group format.[14] Further, patients with symptoms such as dyspnea are at a higher risk due to weather changes, another factor which reduces function and accessibility to interventions that are provided outside the home.[27,37] While home-based interventions during cancer treatment are potentially significant, many do not produce clinically or practically meaningful improvements. For example, while the effects of supervised exercise interventions on the improvement in fatigue are moderate to large (e.g., d=0.75-0.87[50] and d=0.95-1.00), [50-52] the effects of home-based unsupervised exercise interventions are generally small,[53] with standardized mean difference for high-quality studies in meta-analysis being as small as 0.13.[52] Further, limited evidence from quality randomized trials exists to support the use of dietary supplements for fatigue during chemotherapy, with dietary counseling being more promising compared to supplementation. When bundled with exercise interventions, the added benefit of dietary advice does not appear to increase the effect sizes, compared to those reported from exercise interventions alone.[54] Supervised exercise interventions bundled with dietary advice produce moderate to large effect sizes,[55] and self-directed home-based bundled interventions produce small effect sizes.[56-58]

Home-based symptom management interventions in this study, reflexology and meditative practices, have been tested against controls and attention controls in randomized controlled trials, and have been shown to produce moderate to large effect sizes (see preliminary work).[5,32] Each home-based intervention provides a significant strategy to manage fatigue during chemotherapy. However in practice, individual patients vary in their responses to interventions and may try various combinations of symptom management strategies.[59] So the next innovative step after establishing efficacy against controls is individualization and sequencing of interventions using the SMART design.[60,61] The two interventions considered in the proposed research use different approaches; one is physical (reflexology) and one psychological (meditative practices). Therefore the success of these interventions may be different for different patients, and there is a need to either lengthen the time with one therapy or test the effects of adding a different therapy when one does not produce the desired outcomes in a given period of time. The SMART design provides a rigorous framework for such testing because of the strength of conclusions that will be derived from randomized comparisons.

3. Interventions: Two Complementary and Alternative Medicine (CAM) Therapies. An increasing number of cancer patients turn to CAM therapies for symptom management.[62] Our team's program of research focuses on building the evidence base for CAM that may enhance symptom management among cancer patients, in order to determine which therapies warrant translation to practice, and which elicit comfort or placebo effects but do not add to the pool of effective symptom management interventions.[63] The widespread use of complementary therapies in patients is exemplified by a significant increase ($p \leq .001$) over a 7-year time span for common chronic conditions.[64] The National Health Interview Survey reported that 38% of Americans use some type of complementary therapy.[65] The highest users of CAM therapies are younger adult females.[66] Additional factors associated with CAM use vary across studies and include higher education, private insurance, regular exercise, or attending support groups.[66-70] Surveys have found that over time more minority patients are using CAM, with some variation on the types of therapies selected by racial and ethnic underrepresented.[67,68,71] Recent literature also indicates high prevalence of CAM use among men and in low-income urban minority populations.[66] When complementary therapies are used by the public to this extent and without adequate knowledge of safety and efficacy, they run the risk of interfering with conventional health care. Therefore, before complementary therapies can become part of evidence-based symptom management practice, they need to be rigorously tested in RCTs against controls and other therapies, and evidence-based decision rules for best selections and sequences of therapies need to be determined.

The National Center for Complementary and Alternative Medicine (NCCAM)[72] identified five categories of complementary therapies: mind-body; body-based; biologically based; energy therapies; and alternative medical systems. **We have selected a body-based therapy and a mind-body therapy because these two therapy groups are the most widely used by cancer patients,[73] provide different approaches, and both have a demonstrated evidence base against controls.[5,14,74,75]** This evidence is summarized below.

Reflexology. Reflexology is similar to massage in that it manipulates soft tissue for therapeutic purposes, but differs due to the focus on the special areas of the feet called reflexes and the use of a firm thumb-walking motion.[76] It is based on the premise that foot reflexes correspond to organs, glands, and body systems. Stimulating these reflexes may positively affect function of

the target tissue to facilitate health and healing.[76] Current research regarding the impact of reflexology on symptom management is burgeoning.[5] Our team's completed R01 (5R01CA104883-5) demonstrated a significant decrease in fatigue when foot therapy was provided by a lay caregiver.[5] A systematic review of RCTs[77] found that in two cancer studies, reflexology resulted in a significant decrease in anxiety,[78] and a significant improvement in QOL.[79] A second review[80] demonstrated an immediate post-intervention reduction in pain. Since these systematic reviews, five RCTs focused on a cancer patient population. One study reported significantly lower anxiety among multiple types of cancer patients,[81] another found lower pain with a mixed cancer group,[82] a third reported decreased pain among digestive cancer patients,[83] a fourth, using a bundled intervention, found that eight weekly sessions of reflexology plus self-initiated support significantly promoted relaxation among post-surgical early-stage breast cancer patients (n=60),[84] and a fifth study involved a mixed sample of hospitalized cancer patients (n=42) where a partner provided one session, resulting in an immediate decrease in pain intensity and anxiety.[74] Our team completed the first large scale RCT with reflexology (n=385 breast cancer patients), and demonstrated a significant improvement in physical functioning and dyspnea following 4 weekly sessions by a reflexologist.[5] The results from the completed RCT of reflexology and the preliminary results from our nearly completed trial (1R01CA157459-01), where reflexology is delivered by a friend or family caregiver, are presented under justification and feasibility.

Reflexology is a significant body-based intervention selection because it: **1)** is non-invasive; **2)** extremely low risk; **3)** does not interfere with cancer treatment the patient is receiving;[5] **4)** can easily be taught in the home to a friend or family caregiver;[33] and **5)** based on a national survey, patients are highly likely to use it.[85]

Meditative Practices. Meditative practices are purposeful strategies aimed towards building capacities to attend to the present moment, including one's thoughts, emotions, bodily sensations, and the environment with nonjudgmental openness and acceptance.[86] This therapy selection is grounded in evidence that meditation training with gentle yoga and breathing exercises enhance patients' ability to adapt to serious medical concerns.[87-91]

In our completed work presented under justification and feasibility, teaching meditative practices demonstrated feasibility, acceptability and efficacy for symptom management among lung cancer patients.[14,32] Studies that incorporate meditation-based therapies in cancer are increasing and are showing promise in modifying psychological distress and improving HRQOL.[92-94] Such research in cancer groups include studies incorporating observational,[35,95-97] non-randomized prospective experimental,[98,99] and RCT designs.[100-104] Studies in cancer report that training in meditative practices resulted in significant improvements in mood,[105,106] anxiety [31,75,97,101,105,107], depression,[31,75,101,108] fatigue,[36,102,105] HRQOL,[75,98,101] stress,[97,101,108,109] coping,[97,109,110] and sleep quality.[96,99,104] In two RCTs, engagement in meditative practices reduced perceived stress,[103] and psychological distress,[75,105] demonstrating efficacy in modulating emotional symptoms.

Meditative practices are a significant mind-body intervention selection because they: **1)** have been tested with solid tumor cancer patients;[97-99,101,104,110] **2)** are a highly-utilized supportive therapy with vulnerable cancer patients;[75,93] **3)** have been shown to promote adjustment, reduce psychological distress, and improve HRQOL in cancer patients;[94,109] **4)** are economically delivered and feasible for patients to use on their own at home;[94] and **5)** are a non-toxic option for symptom management during active treatment.

Rationale for sequencing of therapies (reflexology and meditative practices). While there are likely several physiological mechanisms involved that contribute to the positive outcomes from reflexology and meditative practices, the benefits derived from reflexology, a direct body manipulation are primarily physically mediated; whereas, the effects derived from training in meditative practices are cognitively-mediated.[91] Reflexology has been implicated in the activation of oxytocin, and to optimize circulatory capacity to eliminate toxins and support immune, nervous, and glandular systems.[84,111] In Magnetic Resonance Image brain scans, meditative practices have demonstrated growth in brain regions that are involved in emotion regulation, attention, learning, and memory function.[112] Both reflexology and meditative practices result in activation of a relaxation response[84,111] characterized by calmness, sensations of wellbeing, and acceptance which may contribute to heightened HRQOL. We will test one therapy, and if it is inadequate, we will either: 1) add the alternative therapy -- recognizing that an alternate therapy may evoke benefits by targeting another pathway to yield the sought benefits, or 2) provide a longer duration of the first therapy. Because of these potential systemic effects, the benefits of reflexology and meditative practices are not limited to immediate results and may be cumulative over time. Therefore extending duration of a single therapy is one possibility to achieve desired symptom reduction. On the other hand, the use of two therapies, that evoke the relaxation response via different pathways to gain similar symptom management, may optimize the potential for therapeutic benefits. Some people may prefer or respond better to a cognitive therapy over direct physical contact, while others may favor body-based reflexology, and the optimal intervention choice and sequencing may depend on such individual differences. The SMART design allows for rigorously testing and tailoring intervention sequences to patients.

4. SMART Design. Existing static symptom management interventions deliver a predetermined dose at specific intervals. These interventions are tested in standard RCTs against controls, and this has already been done for reflexology and meditative practices. Dynamic tailoring of interventions to patient responses is needed to enhance the science of symptom management.[113,114] This gap in science is filled by the SMART design in which we will test interventions that target symptom severity and adjust intensity based on patient response to the management of fatigue. Our approach builds sequences which start with one therapy, and then at a decision point, symptom response is evaluated and one intervention may continue so as to give it more time, or the intervention is intensified by adding a second therapy. If one therapy of 4 or 8 weeks is successful, this information is important for both patient and caregiver who can then target the one best therapy. Other dyads may need the intensity of two therapies. In this case, an important question is whether it is best to start with reflexology or with meditative practices and then add the second therapy, and the proposed research will assess which patient and caregiver characteristics are important in making this decision for future work. While SMART designs do not typically include a control group (since first and second stage interventions have been pre-tested in standard RCTs), we included one to help gauge the clinical significance of improvements in symptoms from sequences of interventions that originate from the first randomization. The evidence obtained in the analysis of the intervention sequences will guide refined algorithms for allocating intervention resources in a way that leads to the best possible patient outcomes.

C. Innovation

The key innovations that maximize the potential of the intervention sequences to improve symptom outcomes are:

1. Involvement of a friend or family caregiver in delivery of a multistage home-based intervention for symptom management over time. Family involvement has been a missing link in sustaining home-based symptom management. Many interventions require delivery by a provider outside of the home and can be expensive. This research creatively utilizes a multistage intervention that builds on evidence established in our work that friend or family caregivers can successfully learn to deliver reflexology and can also participate and/or support patients with their meditative practices over time in nonclinical environments such as the patient's home.

2. Rigorous investigation of combinations and sequencing of therapies. Past research on complementary interventions often bundled several therapies together, and the resulting outcomes could not be attributed to specific therapies.[74,115-118] The proposed study takes a new approach to the rigorous testing of the value added by a second therapy if the first one does not achieve outcomes. The step-up approach with the second randomization provides a design where the effect of intensifying an intervention with a second therapy versus giving a single therapy more time (higher dose) can be isolated.

3. Dynamic delivery model and cutting-edge statistical methods. The innovative SMART design allows us to investigate the sequencing of interventions based on their success with individual patients. Designs similar to SMART have begun to be implemented in chronic conditions[119-122] including cancer,[123,124] and their use for optimizing behavioral interventions has been suggested in PA-13-165[125]that we are responding to. **To our knowledge, this research is the first to use the SMART design for symptom management in cancer patients**. This innovative dynamic delivery model is ideally suited for the temporal nature of symptoms that present challenges to symptom management science.[11,126-128] The exploratory Aim 5 analyses use a Q-learning algorithm to determine optimal decision rules for choosing intervention sequences for individual patients in the future, based on their characteristics and the characteristics of the caregivers who will be providing these home-based interventions or practicing them with the patients. The Q-learning algorithm allows for inclusion of time-varying covariates,[129] such as repeated measures of symptom severity at baseline and over the first 4 weeks, to determine if adding another intervention during weeks 5-8 is warranted. The resulting new clinical decision rules and algorithms have the potential to optimize the delivery of supportive care interventions given individual dyadic profiles.

D. Approach

1. Justification and feasibility

1a. Preliminary Work with Patient Selection of Therapy. In preliminary work, our team administered a 25-item complementary therapy survey to 27 cancer survivors. Strong interest was shown for both mind-body therapies such as meditative practices and body-based physical touch therapies such as reflexology.[130]

We then conducted a quasi-experimental study with 100 mixed cancer patients in active treatment to participate over eight weeks with a family caregiver. Results demonstrated acceptability and feasibility of caregiver participation in complementary supportive therapies.[131]

1b. Preliminary Work with Reflexology. In our recently completed reflexology RCT with 385 women in treatment for breast cancer, no adverse events were reported, and > 89% of women in the reflexology group completed three or four sessions of the four session protocol. Longitudinal comparisons revealed significant improvements in physical functioning for the reflexology group compared to the control group (p=.04). Dyspnea severity was reduced compared with the control (p < .01) and lay foot manipulation (LFM) groups (p = .02). The effects sizes for the improvements in dyspnea and physical function in the reflexology group compared to controls and LFM were medium to large (between 0.41 and 0.87 for average differences between groups over time). No differences were found for depressive symptoms or state anxiety. The LFM group had a significant improvement in fatigue compared to controls (p=.01).[5]

1c. Preliminary Work with Reflexology and Caregivers. In the principal investigators' (PIs) ongoing R01, both patients and their friend or family caregivers are enrolled as dyads in a reflexology study for symptom support and reduction of unscheduled health services used.[132] We have been successful in maintaining scheduled dyad enrollment (N=240 consented and 190 randomized after completing baseline interview as of February, 2015). Friend and family caregivers have been able to achieve protocol proficiency at 90% immediately after training and at the follow-up quality assurance check a week later.[132]

Table 1. Preliminary Work: Reflexology and Caregivers

	Caregiver-delivered reflexology LS Mean (SE) N=72	Attention control LS Mean (SE) N=68	P-value	Effect size
Fatigue severity	3.64 (0.23)	4.32 (0.23)	**.04**	**.46**
Insomnia severity	2.95 (0.26)	3.57 (0.27)	.10	.31
Pain severity	2.25 (0.23)	3.21 (0.24)	**<.01**	**.49**
MDASI total symptom severity	25.07 (1.59)	30.63 (1.63)	**.02**	**.48**
MDASI total symptom interference	12.15 (1.15)	16.08 (1.17)	**.02**	**.48**

After caregiver training, the rate of protocol completion is high for more than one session per week (69%, 89%, 82%, and 83% by week). Virtually all dyads that completed at least one session actually did 2 or more, which indicates the willingness and interest of caregivers in delivering reflexology sessions to patients. Outcomes are measured at baseline, week 5 (post 4-week intervention) and at 11 week follow-up. Analysis included group comparisons at weeks 5 and 11 using linear mixed effects models and estimation of the effect sizes (Cohen's d) for average group differences over time expressed in standard deviation units. The results from N=140 dyads who completed the 5 and/or 11 week interview to date are summarized in Table 1. P-values <.05 and clinically significant effects sizes >0.33 are bolded. The significant improvements due to caregiver-delivered reflexology are seen in severity of fatigue, pain, and summed symptom severity and interference (MDASI).

1d. Preliminary work with meditative practices. To develop our meditative practices intervention, we first conducted focus groups with cancer patients who had undergone radiation (RT) and chemotherapy.[14]

Table 2. Preliminary work with Meditative Practices

	Meditative practices LS Mean (SE)	Attention control LS Mean (SE)	P-value	Effect size
SF-36 Vitality (lack of fatigue)	47.92 (2.19)	44.15 (2.06)	0.24	**0.45**
Total Dyspnea Score	3.64 (1.07)	7.60 (0.99)	**0.02**	**0.96**
SF-36 Bodily Pain	48.89 (2.39)	44.93 (2.25)	0.26	**0.41**
Cancer Worry	6.17 (0.53)	8.07 (0.49)	**0.02**	**0.85**
Depressive symptoms (CESD)	7.84 (1.80)	12.76 (1.68)	0.07	**0.70**
Sleep Quality Problems	8.38 (1.87)	11.76 (1.75)	0.22	**0.45**

Based on the findings from these focus groups, we developed a shortened home-based intervention responsive to the needs of vulnerable cancer patients who are in treatment. The adapted meditative practices protocol was tested with 40 patients with lung cancer [mean age: 66.2±9.4 years; sex: 27(67.5%) females, 13(32.5%) males; disease stage: III, 10(25%); IV, 30(75%)] receiving radiation and/or chemotherapy. Patients were randomized to receive weekly meditative practice sessions (N=20) or an attention control condition (N=20). Outcomes were measured at baseline, post intervention and at 11 weeks. Table 2 summarizes the least squares (LS) means, their standard errors (SE), p-values and adjusted effect sizes for group comparisons. Due to relatively small sample size, statistical significance was not reached for all outcomes; however the effect sizes indicate clinically significant improvements and the magnitude of the effect sizes is similar to those seen in Table 1 for the reflexology intervention. The study demonstrated feasibility of our adapted meditative practices program, and early efficacy with respect to symptom reduction.[32]

2. Team. Our team is led by Co-PIs Drs. Gwen Wyatt and Alla Sikorskii. Dr. Wyatt is a professor in the College of Nursing, whose research program focuses on testing complementary therapies as supportive care interventions for cancer patients to lessen symptoms and enhance HRQOL.[130,131,133-142] She is currently PI on a NCI 1R01 (CA 157459-01) involving reflexology and a friend or family caregiver; she is also Co-I on an acupressure study with breast cancer survivors (1R01 CA151445-03); and has completed a reflexology RCT (1R01 CA104883-01A1) with breast cancer patients. Dr. Sikorskii is an associate professor in the Department of Statistics and Probability, statistician and methodologist who has collaborated with Dr. Wyatt since 2004 and is currently a Co-Investigator (Co-I) on the ongoing reflexology R01. In addition to the ongoing reflexology RCT, Dr. Sikorskii has served as a Co-I on 10 NIH funded R01 grants and one large CDC-funded study. The multiple PI leadership is essential to the proposed project that requires expertise in symptom management and complementary interventions as well as expertise in design and methodology of intervention testing. Co-I Dr. Rebecca Lehto is an assistant professor and expert oncology clinician who investigates meditative practices in cancer patients to facilitate improvement of cognitively-mediated symptoms. Our team consultants are: Elizabeth Marazita, a Doctor of Oriental Medicine and reflexology expert; and Denise Kozikowski, PhD who is a psychologist and certified expert in meditative practices.

Other Personnel. Recruiters will be located at each site. Interviewers will contact participants via telephone at baseline and week 12 from the main research office. Intervention experts will train and QA the study reflexologists and meditative practices teachers; study reflexologists will train caregivers in reflexology and meditative practices teachers will train caregivers in meditative practices. The Education Coordinator (EC) will schedule and coordinate all training, and make weekly calls to caregivers.

3. Setting. We will begin with 3-4 oncology clinics in the Midwest, and open additional sites if needed to maintain enrollment. All dyad therapy sessions will be done in the home.

4. Sample. Patients will be approached at the participating oncology clinics. Inclusion criteria are: **1)** age 21 or older; **2)** solid tumor cancer diagnosis; **3)** able to perform basic activities of daily living; **4)** undergoing chemotherapy, hormonal therapy, or targeted therapy; **5)** reporting severity of ≥3 on fatigue using a 0-10 standardized scale at intake; **6)** able to speak and understand English; **7)** have telephone access; and **8)** able to hear normal conversation. Exclusion criteria are: **1)** diagnosis of major mental illness in medical record and verified by the recruiter; **2)** nursing home resident; **3)** bedridden; **4)** currently involved with reflexology or meditative practices; or **5)** deep vein thrombosis or painful foot neuropathy.

Solid tumors have been selected because fatigue can be effectively managed with the two interventions based on existing evidence, and this symptom is prevalent during cancer treatment.[5,143,144] The cut-off of ≥3 indicates a moderate level of fatigue based on established interference-based cut-points.[145] Virtually all solid tumor cancer patients on chemotherapy reach a threshold of 2 or higher on fatigue at some point, and the cut-off of 3 was found to be optimal in past work for balancing sensitivity and specificity in the prediction of the need for symptom management in the future 8 weeks.[146]

Friends/family caregivers will participate with each patient and will complete a consent form. Their inclusion criteria are: **1)** age 18 or older; **2)** able to speak and understand English; **3)** access to a telephone; **4)** able to hear normal conversation; **5)** cognitively oriented to time, place and person (determined via recruiter); and **6)** willing to be trained in reflexology and meditative practices.

4a. Sample size. To determine the sample size for this study, we started at the right end of the schematic in Figure 1 (the second randomization) and moved from right to left to determine the needed number of consenting patients. To power the comparisons for the value added by reflexology or meditative practices, we used the effect size of 0.45, the smaller of the two effects sizes for fatigue from Tables 1 and 2 to conservatively estimate sample size requirements. The effect size of 0.45 corresponded to 2 repeated measures in past work, and the design of this study includes 4 repeated measures at each phase. Assuming a correlation of 0.4 among repeated measures seen in past work, the adjusted effect size for the longitudinal analysis of 4 time points is 0.54, which results in the sample size requirement of N=55 per group being compared (far right of Figure 1), for power of .80 or greater in two-tailed tests at 0.05 level of significance. These 55 patients from 4 groups (220 total) created by the second randomization will be non-responders from the first intervention stage. Assuming that these 220 are 80% of the total number of patients in the first stage (i.e., that there is a 20% response rate to fatigue during the first 4 weeks), we will need 276 patients to be randomized to interventions. The size of the control group was selected to be 55 to maximize power in the comparisons with intervention subgroups. Therefore the total required post-attrition sample size is N=331. To account for 23% attrition seen in past work[5,147] with solid tumor cancer patients, we will need to have 430 patients consent.

4b. Strategies to minimize sample attrition. 1) Recruiters will emphasize the importance of participating in the full intervention and the weekly calls; 2) patients will be asked to mark their home calendar for intervention days and study calls; and 3) weekly calls to patients maintain contact for the entire study duration. These strategies have worked well in our completed and ongoing trials.

Participants will be assured of the confidentiality of all information and that refusing to participate will not alter their care. Patients will continue to receive standard medical care, so if any healthcare problems arise, they may seek care from their health providers. For patients who refuse, the recruiter will seek consent to review their record for demographics and ask the reason for refusal. These data help us understand who declines and contribute to external validity and generalizability of the findings.

5. Recruitment. Our team has an existing relationship with 14 oncology clinics in the Midwest. Even with recruitment challenges,[148] we are confident of achieving the recruitment target of 430 before attrition, and a post-attrition sample size of 331. In our recently completed reflexology R01 (N=385 breast cancer patients), we were able to remain within 10% of recruitment goals for the four years of enrollment and had a consent rate of 74%. In our current R01 with both cancer patients and their caregivers (planned N=200 patients; 200 caregivers post-attrition), we are having similar enrollment rates during year four. As of February 2015, N=190 dyads have completed baseline interview and were randomized. Our samples are representative of the cancer patient populations in the Midwest. In the most recent reflexology trial, 14% of patients and 13% of caregivers were African American, and 4% were Hispanic.[33]

5a. Accrual. Recruiters have research roles and do not provide direct care at the sites. They will approach patients during clinic visits and explain the study. Patients can choose to consent at that time if their caregiver is present, or take the packet home to discuss with their caregiver. 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 verbal consent is obtained over the phone for either the patient or caregiver, the consent forms in the packet can be signed and returned in the stamped envelope. If the consent forms are not returned within one week, the recruiter will call as a reminder to mail the consent forms if they wish to participate.

5b. Recruiter training includes didactic information, role-playing, problem cases and return-demonstration conducted by the study Education Coordinator at sites. Recruiters will use a script to introduce the study to patients including: **1)** initial randomization to reflexology, meditative practices for symptom management or a usual care control group, and the possibility of the two active groups being re-randomized after 4 weeks of using the first therapy to either continue the same therapy or to also add the other therapy; **2)** weekly intervention sessions provided by their caregiver in the two active groups (following training by a reflexologist and/or a meditative practices teacher) in their home; **3)** there is no cost; **4)** the complete study lasts 12 weeks to include all data collection (i.e., weekly calls and two 30-45 minute phone interviews); **5)** both therapies are designed to help reduce symptoms and improve HRQOL; and **6)** a review of potential risks/benefits.

6. Randomization. Following the baseline interview, patients will be randomized to reflexology, meditative practices or standard care control. Randomization will be completed using a computer minimization algorithm programmed by Dr. Sikorskii that balances arms by recruitment location, site of cancer, stage of cancer (early versus late) type of treatment (chemotherapy, hormonal therapy or targeted therapy, and their combinations), patient sex and relationship to the caregiver (spouse vs non-spouse).[149] The second randomization will occur for those who do not respond on fatigue to the therapy received after the first 4 weeks of therapy. The second randomization will be implemented using the same approach as the first, with the same balancing factors, except that randomization will allocate patients into 2 groups: continuing the same therapy or adding the other one.

7. Intervention Components

7a. Active Group Caregiver Intervention Procedures. Caregivers will: **1)** be trained by a study reflexologist or meditation teacher in the therapy their patient is initially randomized to; **2)** after 4 weeks of delivering the therapy, caregivers will be trained in the second therapy if their patient is re-randomized to receive the other therapy; **3)** receive weekly calls over 8 weeks to maintain fidelity and inquire about the number of sessions completed in the past 7 days. At least one weekly session is required per protocol. The number of additional sessions per week is not restricted in a home-based intervention, and the number of sessions delivered is tracked weekly (see 7d, Protocol Fidelity).

7b. Intervention Protocols. As recommended by the NCCAM, complementary therapy investigators should partner with therapy experts, while acknowledging that the investigator role requires very different preparation than that of the practitioner.[150] Our team has successfully maintained this role delineation and will again engage leading experts to assure protocol fidelity and delivery. Consultant Dr. Elizabeth Marazita, reflexology expert, will oversee the protocol via start up and annual consultation with Dr. Wyatt and our training reflexologists. Consultant Dr. Denise Kozikowski, meditative practices expert, will oversee the protocol via start up and annual consultation with Co-I Dr. Lehto and our training meditation teacher (see experts & trainers letters of support). The consultants and trainer for each therapy will have no direct contact with participants; this further assures protection against contamination of roles.

7c. Common Elements to Study Provider Training. The intervention trainers will train the study providers who will work directly with patients and caregivers. Study provider reflexologists will be practicing reflexologists, who will be trained in the study specific protocol. Study meditation providers will be health professionals, e.g., nurses. Training for both therapies will include didactic information, written steps of the protocol, role-playing, demonstrations, and return-demonstrations based on our study-specific criteria. All study providers must demonstration protocol proficiency $\geq$ 90% to begin and continue (QA checks) with participants (proficiency check list in appendix). Both therapies have written instructions with diagrams that will be left with caregivers. In addition, to enhance the utilization of technology, a DVD demonstrating the instructions will be offered to all dyads. Each study provider will be in the home approximately 45-60 minutes during the first two weeks of the caregiver using the therapy. The first visit is for training and the second to observe and smooth out any errors. This method of caregiver involvement is working well in our ongoing R01.[132] All caregivers will be expected to involve the patient in a minimum of one session per week. Study providers will help the patient and caregiver select a day and time each week for the home-based session.

7d. Protocol Fidelity and Number of Sessions Per Week. Intervention protocol fidelity will be assured through established methods outlined by the NIH Treatment Fidelity Workgroup on consistency in dose, providers, delivery, receipt and enactment of the intervention.[151] Consultants, Drs. Marazita and Kozikowski will assure fidelity through maintenance of the protocol and its delivery. If questions or concerns arise regarding protocol fidelity, the respective expert will be consulted for assistance and advice. *Dose Consistency*. Initially all patients randomized to intervention groups will have four weeks of either reflexology or meditative practices with their caregiver. Weekly sessions for each of the two therapies will be approximately 45-60 minutes long. Symptom data from the first four weeks will then be evaluated to determine which therapy the dyads will continue with through week 8. *Provider Consistency*. All study providers will pass a demonstration of $\geq$ 90% proficiency as judged by

the trainers' score on the checklist for both therapies before beginning with caregivers. Caregivers must also achieve 90% accuracy. *Delivery Consistency*. There will be a QA check and booster session conducted biannually for each study provider (those who teach caregivers one or both therapies), with a 90% proficiency in delivery of the therapies. Caregivers are taught and evaluated during intervention weeks 1 and 2. If taught the second therapy after week 4, training and evaluation occurs again at weeks 5 and 6. *Receipt and Enactment Consistency*. The caregiver will also be called by the Education Coordinator every seven days and asked the number of completed sessions since the last weekly call seven days ago. A minimum of 1 session is required, but the exact number of sessions reported by the caregiver will be recorded weekly. Thus, fidelity of the receipt and enactment of each therapy will be documented weekly over the 8-week intervention period.

7e. Incentives. All participants will be mailed a thank-you letter and a local complementary therapy directory after the week 12 data collection. Control caregivers will be offered a complimentary training session of their choice (reflexology or meditative practices). This therapy-based incentive has worked well in the past.[132,152]

8. Data Collection

8a. Interviews. All patients and caregivers in intervention and control groups will have data collected twice via telephone interviews: baseline and study week 12 to capture post-intervention effects. Study measures have published evidence of reliability and validity with samples of cancer patients and caregivers. The interviews will take 30-45 minutes. If a participant becomes fatigued, we will divide the telephone interview into two phone calls within the same week.

8b. Interviewer Training. The interviewers will call both members of the dyad at intake and week 12. Interviewers will be blinded to the dyad's group assignments. The Education Coordinator will train interviewers via didactic information, written steps, role-playing for difficult interview questions, and return-demonstrations based on our study-specific criteria. In addition, 10% of all interviews will be recorded for QA.

8c. Weekly Calls to Patients. The interviewers will make the weekly calls to all patients to assess symptoms using MDASI (fatigue included) during the 8-week intervention period or an equivalent time frame for the control group. Therefore the attention of asking patients about their symptoms will be equalized across groups. When a symptom is rated at a 7 or higher on the 0-10 scale, patients will be asked to contact their oncology office. For patients randomized to reflexology or meditative practices, weeks 1-4 call data will be used to assess response on fatigue (see definition of symptom response below). If response is not achieved; the patient and caregiver will be re-randomized and weekly calls will continue for weeks 5-8 in the intervention and control groups. The weekly calls will provide documentation of the process of change in symptoms.

8d. Weekly calls to Caregivers. Each intervention caregiver will be called by the Education Coordinator every 7 days to assess the number of sessions conducted with the patient since the last call 7 days ago, as described under Fidelity (section 7b). During weeks 5-8, if re-randomized to add another therapy, the number of sessions will be recorded for the initial and added therapies. The Education Coordinator will make these calls because interviewers need to be blinded to dyad's group assignments.

9. Measures of Primary Symptom Outcome - Fatigue

9a. Brief Fatigue Inventory (BFI) [153] *(Patients; baseline & week 12).* Physical and emotional components of fatigue will be measured with the Brief Fatigue Inventory for rapid assessment of fatigue severity and interference with daily life. The instrument consists of nine items. The first three items ask respondents to rate the severity of fatigue "right now," at its "usual" level during the past 24 hours and at its "worst" level during the past 24 hours. Answer choices are on a scale of 0 to 10, where 0=no fatigue and 10=as bad as you can imagine. The remaining six items assess how fatigue affected the following during the past 24 hours: general activity, mood, walking ability, normal work (including work outside the home and daily chores), relations with other people, and enjoyment of life. Responses are on a 0 to 10 scale where 0=does not interfere and 10=completely interferes. Alpha coefficients exceeded .95.

Table 3: Measures

Patient Measures	Week 1	Week 12	Weekly calls
1.a Primary Outcome			
• Physical and Emotional Fatigue (Brief Fatigue Inventory)	X	X	
• Cognitive Fatigue (Attentional Function Index)	X	X	
1.b Secondary Outcomes			
• MDASI minus fatigue to avoid redundancy with BFI	X	X	
• PROMIS Depression & Anxiety SF 4	X	X	
1.c Weekly Calls			
• MDASI with fatigue, since no BFI or AFI in brief weekly calls			X
2. Potential Covariates			
• Patient Demographics	X		
• Bayliss Tool (Chronic Conditions)	X		
• Medical Chart: Symptoms & Conditions		X	
• Complementary Therapy Expectancy Scale	X		
• Complementary Therapy Utilization	X	X	
• Satisfaction with Caregiver Involvement Survey		X	
Caregiver Measures			
1. Potential Covariates			
• PROMIS Profile 29	X	X	
• Caregiver Demographics	X		
• Caregiver Reaction Assessment Tool	X	X	
• Complementary Therapy Expectancy Scale	X		
• Number of Weekly Sessions Completed			X

9b. Attentional Function Index (AFI) (Patients; baseline & week 12).[154] The cognitive component of fatigue will be assessed with the 13-item AFI which measures perceived effectiveness in essential daily challenges that require optimal cognition, and has shown consistent reliability in adults with breast cancer.[154,155] In our previous studies with lung cancer, alpha reliabilities were .89 and .91 respectively.[156]

10. *Measures of Secondary Symptom Outcomes.*

10a. Symptom Inventory (Patients; baseline & week 12 & weekly calls).[157] The expanded M.D. Anderson Symptom Inventory (MDASI) evaluates severity of 19 symptoms experienced by cancer patients (i.e., fatigue, pain, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering, decreased appetite, drowsiness, dry mouth, sadness, vomiting, numbness/tingling, diarrhea, constipation, sore mouth, rash, hair loss, and cough, and the interference of these symptoms with daily life on the scale from 0=symptom not present to 10=worst imaginable. This instrument has established evidence of reliability and validity in samples of cancer patients.[158] It has been recently updated to include the most common symptoms experienced by patients undergoing modern cancer

treatments.[25] A **single summed** symptom severity score across 18 symptoms (without fatigue, since it is measured in more detail by the BFI and AFI as described in item 9 above) will be used as a secondary outcome in study Aims 1-4 and in building optimal decision rules in exploratory Aim 5.

10b. & c. Measures of Secondary Outcomes of Depression and Anxiety. PROMIS-short forms 4: depression and anxiety (Patients; baseline and week 12).[159-162] These two symptoms are not directly covered by MDASI, which includes related items of distress and sadness. Therefore, we include the additional PROMIS measures for these symptoms. PROMIS measures were developed using sophisticated measurement techniques, including Item Response Theory (IRT).[159,163] Testing in more than 21,000 individuals from the U.S. general population has resulted in individual item calibrations that produce t-scores for the general population. The available short forms have evidence of reliability and validity, and have high correlations with IRT-derived scores obtained from extensive item banks. We chose 4-item short forms to minimize respondent burden while maintaining measurement precision.

11. Determination of Response on Fatigue during Weeks 1-4 for the Purpose of Re-randomization *(Patient; weekly calls)*. Fatigue response will be assessed based on the fatigue item from MDASI administered in weekly calls to patients. First, we define symptom onset as the date of the weekly call when a symptom for the first time is reported by the patient as moderate or severe according to established and validated cut-points.[145] The cut-points mark the places on a 1-10 severity scale where largest increases in symptom interference occur as severity increases between successive integers ranging from 1 to 10. Thus, the cut-points are anchored in symptom interference with patient's lives. For fatigue, the mild category corresponds to a severity score of 1, moderate category corresponds to scores 2-4, and scores of 5-10 fall into the severe category. Note that the cut-off score of 3 or higher in the inclusion criteria means that at intake patients experience fatigue at a moderate or severe level. Patients who started at severe at onset and ended at moderate or mild by the 4 week observation, and patients who started at moderate and ended at mild, will be called **responders** on fatigue.[164] Since responders demonstrate a substantial improvement anchored to fatigue interference with daily life after 4 weeks, they will continue with the intervention for another 4 weeks. Patients who remain at moderate levels or move to severe at week 4 will be classified as **non-responders**.[145,165,166] These patients will be re-randomized to either continue with the same therapy, or add the second therapy, in order to rigorously test the value added by the second therapy in Aims 2 and 3.

12. Measures of Dyad Characteristics (Potential Covariates)

12a. Demographics (Dyads; baseline). Demographics include age, education, work, ethnicity, race, religious affiliation, marital status, and relationship between patient and the friend or family caregiver.

12b. Chronic Conditions (Patients; baseline). The Bayliss tool queries the presence of 20 comorbidities.[167]

12c. Medical Treatment (Patients; eligibility & week 12). Chart data include radiation, surgery, chemotherapy (dose, type, dates received), co-morbidities, cancer stage, and medications (e.g., supportive agents for pain control, nausea, anxiety, or depressive symptoms) corresponding with the time-on-study. In addition, the Common Terminology Criteria for Adverse Events (CTCAE) data will be collected on side effects and toxicities including anemia and neutropenia.

12d. Complementary Therapy Expectancy Scale (Dyads; baseline).[168] This tool has items on logical thinking and feelings related to complementary therapy use.

12e. Complementary Therapy Utilization (Patients; baseline & week 12).[169] Assesses the use of 24 therapies.

12f. Caregiver Reaction Assessment Tool (Caregiver; baseline and week 12).[170] Caregiver burden will be measured with this tool 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.

12g. PROMIS Profile-29 (Caregivers; baseline & week 12).[159,171] The PROMIS profile instruments are a collection of profile short forms, containing items from one of seven primary PROMIS domains (depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and satisfaction with participation in social roles). The PROMIS Profile-29 includes four items from each primary domain plus a single pain intensity rating. The instrument was developed for the general population and is particularly suitable for the assessment of caregiver health, including symptoms and functioning. Since interventions will be delivered by or practiced with the caregivers, caregiver health may influence the optimal decision rules explored in Aim 5.

12h. Patient Satisfaction with Friend or Family Caregiver Involvement. (Patients; week 12).[172] *This survey consists of 5 items that query patient satisfaction with their caregiver involvement.* Since the week 12 patient survey is unique for the purposes of this study, it has not been validated with other samples previously. Formal psychometric evaluation will be performed during analysis by Co-PI Dr. Sikorskii who has extensive expertise in measurement.[173-176]

13. Protocol Integrity Assessments

13a. Therapy Protocol adherence will be evaluated by the number of completed sessions per week. The Education Coordinator will call the caregiver every seven days and fills out a session form at the end of each weekly call which includes adherence and number of completed sessions during the past seven days.

13b. Attrition Data will be documented when it occurs in association with data collection interviews, including being unable to reach the patient or the patient stating she/he wishes to discontinue. The date and reason, when possible, will be documented. Interviewers will make three attempts for each call.

13c. Training Forms for proficiency will be completed at each training and refresher**.** The trainers for the reflexologist and meditative practices providers will use a scored proficiency checklist to test study providers accuracy initially and at QA checks every 6 months. Study providers will also use the proficiency checklist when training caregivers at weeks 1 & 2 and if a second therapy is added at weeks 5 & 6.

14. Analytic Methods

Data management, tracking and analyses. All data for patients will be entered into the secure web-based database that will be accessible to recruiters and interveners at multiple recruitment sites. To maintain security, data will be stored within a server different from the server of web application. Periodic quality assurance checks of the data will be performed. De-identified data will be transferred into SAS 9.4 for analyses.

14a. Baseline Comparisons and Regression Techniques. To check the baseline equivalence of groups created by the first randomization and the equivalence of subgroups created by the second randomization, the outcome values at baseline and potential covariates will be compared using t-tests, chi-square or Fisher's exact tests. The latter variables include recruitment location, age, sex, site and stage of cancer, type of treatment (e.g., chemotherapy and/or radiation, hormonal therapy, targeted therapy), administration of supportive agents, comorbid conditions, relationship to the caregiver, and living arrangements. If systematic differences are discovered, then the appropriate variables will be included as covariates in further analyses. 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. Two-sided tests of hypotheses stated below will be performed to determine the superiority of one group versus another as created by first and second randomizations.

14b. Attrition Analyses and Handling of Missing Data. We will compare dyadic characteristics of those who drop out between consent and first randomization to those who continue participation. Following the first randomization, attrition analyses will compare those who drop out according to the second randomization. In addition, we will compare characteristics of those who completed the study with those who did not within their designated group to inform the generalizability of findings. The regression techniques described below allow for missing at random (MAR) mechanisms.[177] 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).[178,179] Since NMAR or MAR assumptions are not directly testable, we will employ sensitivity analyses to investigate the robustness of the results under pattern-mixture or other models.

Primary Analysis outcomes: severity of fatigue (primary, physical and emotional from BFI, cognitive from AFI), summed severity index of other symptoms (secondary, from MDASI), depression (secondary, from PROMIS), anxiety (secondary, from PROMIS).

Aim 1, part a), relative effectiveness of reflexology and meditative practices.

Hypothesis 1. Patients randomized to the reflexology group will report lower severity of fatigue and lower summed severity score from the MD Anderson symptom inventory at weeks 1-4.

This hypothesis will be tested using statistical model #1 that relates the outcome *y* at weeks 1-4 to the group assignment variable x_1(reflexology, meditative practices or control), outcome at baseline x_2, and other covariates (see baseline comparisons). Additional covariates will include variables used in randomization, due to their potential impact on outcomes. If errors are normally distributed, this model will be fit as a linear mixed effects model (LME), which generalizes classical analysis of repeated measures. Generalized linear mixed effects (GLME) modeling will be used with the appropriate link function and error distribution (e.g., gamma) if the symptom severity outcome is not normally distributed and cannot be normalized using transformations. We are primarily interested in the additive effect of the group variable, and differences in the least square (LS) means will be tested according to the levels of variable x_1.

Aim 1, part b), characteristics of responders and non-responders. Patients who are responders or non-responders on fatigue will be defined as described in measures. The characteristics of

responders and their caregivers will be compared to those of non-responders using t-tests, chi-square or Fisher's exact tests.

Aim 2, Hypothesis 2. Patients who do not respond to reflexology on fatigue during weeks 1-4 (1st intervention stage) and have the meditative practices added during weeks 5-8 (2nd intervention stage), will report lower severity of fatigue and improved 3 secondary outcomes: summed severity index of other symptoms, depression and anxiety, as compared to those who are re-randomized to continue with reflexology alone.

The analytic strategy described under the analyses for Aim 1 will be implemented for the comparison of two groups created by the second randomization. The repeated severity measures during weeks 5-8 and week 12 will be related to study group (reflexology alone versus reflexology and meditative practices), symptom severity during week 4, and covariates (see preliminary analyses). The test of the significance of the coefficient for the group variable will yield a formal test of Hypothesis 2 for the severity of fatigue and other symptoms. PROMIS measures of depression and anxiety obtained in the week 12 interview will be analyzed using general or generalized linear models, and the test of Hypothesis 2 for these 2 secondary outcomes will come from the significance of the coefficient for group assignment in the second randomization.

Aim 3, **Hypothesis 3.** Patients who do not respond to meditative practices on fatigue during the weeks 1-4 (1st intervention stage) and have the reflexology added during the 2nd intervention stage (weeks 5-8), will report lower severity of fatigue and improved 3 secondary outcomes: summed severity index of other symptoms, depression and anxiety as compared to those re-randomized to continue with meditative practices alone.

The analysis for this aim is the same as the analysis for Aim 2, but will be performed among those who did not respond to meditative practices during weeks 1-4.

Aim 4, Hypothesis 4: Patients randomized to intervention sequences beginning with reflexology or meditative practices will report lower severity of fatigue and improved 3 secondary outcomes: summed severity of other symptoms at weeks 1-8 and week 12, depression and anxiety at week 12 compared to controls.

The LME model described under analysis for Aim 1 will be extended to include 8 repeated measures of symptom severity (from weekly calls) and an additional measure from week 12 interview. The test of significance of the explanatory variable reflecting the results of the first randomization will yield a formal test of Hypothesis 4. PROMIS depression and anxiety measures from week 12 interview will be analyzed using generalized linear models with the following explanatory variables: group assignment at first randomization, depression or anxiety (respectively) at baseline, and balancing variables from randomization.

Exploratory Analysis: Aim 5.

To explore which dyadic characteristics observed during weeks 1-4 are associated with optimal patient symptom outcomes at weeks 5-8 and week 12, so as to determine additional tailoring variables for the decision rules of selecting the first intervention stage and switching from the first intervention stage to the second.

The analyses for this aim will help build optimal intervention sequences by determining the optimal decision rule (d_1, d_2) specifying best first and second intervention stage. This determination is not as simple as determining the best intervention at each stage ignoring future interventions. Such simplistic approaches would ignore longer-term effects of the intervention which was inferior at stage 1, but produced better outcomes in a longer term if simply continued versus combined with another intervention. The analysis approach to this aim therefore follows the maximization method called Q-learning.[167,180-182] The Q-learning algorithm proceeds from right to left in Figure 1, i.e. backwards from the last decision to the first. Two Q-functions will be considered. The function $Q_2(H_2) = E[Y_2|H_2]$ is the expectation of the second stage outcome Y_2 given history after 2 stages, denoted by H_2: dyadic characteristics, outcomes observed during weeks 1-8 and week 12, and interventions received. The function $Q_1(H_1) = E[Y_1 + \max Q_2(H_2)]$ uses history through the first intervention stage H_1.The conditional expectations in the Q-functions will be estimated from regression analyses for the outcomes of severity of fatigue, summed severity of other symptoms, depression & anxiety, and the optimal decision rule will be found using backward induction by maximizing these functions.[183,184] Due to caregiver involvement in intervention delivery, caregiver characteristics including measures of symptoms (described in the measures section) will be explored, as the optimal decision rules may be based on both patient and caregiver factors. The Q-learning method will be implemented in SAS PROC QLEARN[129] developed by Murphy and colleagues.[185] The procedure uses a generalization of Q-learning, which allows treatments and covariates to vary over time, a feature especially relevant to this trial that has weekly symptom assessments. Using this procedure, we will identify tailoring variables that can be used to operationalize the decision rules of selecting the first intervention and switching from the first intervention stage to the second. These decision rules can then undergo testing in a future confirmatory RCT.

15. Potential Difficulties/Limitations and Alternative Approaches

Since 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. One primary (fatigue), 3 secondary outcomes (summed severity of other symptoms, depression & anxiety) and the hypotheses are all stated a priori. In the exploratory analyses, the issue of multiple testing will be addressed by employing the Benjamini-Hochberg or Hochberg adjustment[186-188] to control for the false discovery rate. Because multiplicity adjustments are controversial, all results will be presented both adjusted and unadjusted.

Table 4. Timeline

Months	1-6	7-12	13-18	19-24	25-30	31-36	37-42	43-48
Contracts, site IRBs, manuals, training, database programming	X							
Enrollment, interviews, interventions, medical record audits		X	X	X	X	X	X	
Conduct QA, data safety and attrition monitoring		X	X	X	X	X	X	
Set up for analysis, conduct analysis, report		X		X		X		X

16. Data Sharing

Findings from this study will be available to other researchers under the following conditions: 1) appropriate human subjects protection is in place; 2) data have been de-identified; and 3) study investigators have publicly presented and published key findings.

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