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Using SMART Design to Improve Symptom Management among Cancer Patients:

A Study Protocol

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Abstract

This in-progress sequential multiple assignment randomized trial (SMART), with 331 (post-attrition) dyads of solid tumor cancer patients and their caregivers initially randomizes patients to 4 weeks of reflexology or meditative (mindfulness) practices provided by/with their caregiver in the patient's home, or to a control group. Dyads where patients do not improve on fatigue (non-responders) after 4 weeks are re-randomized to either provide additional time with the single therapy during weeks 5-8, or to add the other therapy. The aims are:

- 1) To compare the reflexology and meditative practices groups during weeks 1-4 on patients' fatigue severity, summed symptom inventory score, depressive symptoms, and anxiety, so as to determine: a) the relative effectiveness of these therapies; and b) the characteristics of responders and non-responders to each therapy.
- 2) Among reflexology non-responders on fatigue severity during weeks 1-4, to determine the value added by meditative practices during weeks 5-8 vs continuing with reflexology alone for patient symptom outcomes.
- 3) Among meditative practices non-responders on fatigue severity during weeks 1-4, to determine the value added by reflexology during weeks 5-8 vs continuing with meditative practices alone for patient symptom outcomes.
- 4) To compare improvements in patient symptom outcomes among three groups created by the first randomization.
- 5) To explore which dyadic characteristics are associated with optimal patient symptom outcomes, so as to determine tailoring variables for the decision rules of sequencing future intervention stages.

The trial currently has N=150 dyads enrolled and is successfully overcoming challenges with dyadic recruitment and retention, while maintaining fidelity.

Introduction and Background

The Precision Medicine initiative aims to overcome the “one size fits all” approach to health care to identify treatments best suited for individuals (National Institutes of Health, 2015). The National Institutes of Health (NIH) has encouraged use of novel research designs such as the sequential multiple assignment randomized trial (SMART) that includes sequences of treatments as opposed to single fixed treatments (Collins, Murphy, & Bierman, 2004). The need for testing such sequences arises from clinical practice, where a clinician selects treatments based on the available evidence. If the initial treatment does not work, clinical logic includes allowing more time, adding supplemental modalities, or switching to different treatments. However, these decisions are often not evidence based, and the decision rules may be implicit and difficult to replicate (Song, DeVito Dabbs, & Ward, 2016).

The dynamic model of sequencing alternative treatments depending on observed success is ideally suited for the temporal and concurrent nature, and varying etiologies of multiple symptoms that present complex challenges to symptom management science (Kroenke, 2001). The burden of symptoms resulting from cancer and its treatment that contribute to diminished health related quality of life (HRQOL) has been well documented (Badger, Segrin, & Meek, 2011; Brant, 2016; Cleeland et al., 2013a). Existing static symptom management interventions deliver a predetermined dose at specific intervals and are tested in standard randomized controlled trials (RCTs) against controls. When overall efficacy of an intervention is established, heterogeneity may still exist in patient responses, which is addressed in the literature by considering moderators of treatment outcomes that define groups of patients who benefit from interventions differentially (Kraemer, Wilson, Fairburn, & Agras, 2002; Sikorskii et al., 2015). While the identification of moderators is one step toward accounting for heterogeneity, the next

step of intervention sequencing and tailoring is needed to advance intervention science (Knobf et al., 2015), and the science of cancer symptom management in particular. In this SMART design approach, we rigorously test the adjustment of intervention type and/or duration through sequencing, which is based on patient response.

Methods

Conceptual framework

Fatigue is the most prevalent and often distressing symptom related to cancer and its treatment (Armes, 2004). The adapted Barsevick symptom management model (Barsevick et al., 2010) guides this study. In this model, fatigue is defined through subjective experience of weariness, tiredness, and low energy, and objective experience through perceived impact on physical, cognitive, and psychosocial functioning. Improved management of fatigue (primary outcome) is the proposed mechanism for improving HRQOL. This improvement will be achieved by sequencing two evidence-based interventions in this trial.

Overview of the SMART design

The SMART design of this study is summarized in Figure 1 and stems from over a decade of methodological research approaches for multi-stage designs (Chakraborty & Murphy, 2010; Collins et al., 2004; Rush et al., 2003; Schneider et al., 2001; Thall, Millikan, & Sung, 2000; Wahed & Tsatis, 2004). For the first intervention stage, dyads (patients with solid tumor cancer and their caregivers) are randomized to 4 weeks of reflexology or meditative (mindfulness) practices provided by/with their caregiver in the patient's home, or to a control group, with weekly assessments of patient symptoms (all groups) and intervention fidelity (intervention groups). For the dyads where patients who do not improve on fatigue (non-responders), based

on 4 weekly assessments, a 2nd randomization is performed to either provide additional time with the single therapy during weeks 5-8, or to add the other therapy (reflexology or meditative practices, respectively) to facilitate patient symptom management, continuing with the weekly assessments of symptoms and intervention fidelity. Adding the second therapy may result in better symptom management, or prove to be too intensive and burdensome for the dyad. This research will make this important determination and identify the best first and second stage therapies given dyadic characteristics. The sustainability of use of these two evidence-based therapies and improvements in symptom outcomes are tested against controls during weeks 5-8 and at study week 12 follow-up of 331 (post-attrition) dyads.

Specific aims and hypotheses

Aim 1. To compare the reflexology and meditative practices groups weeks 1-4 (1st intervention stage) on the primary outcome of patient's fatigue severity and 3 secondary symptom outcomes: summed symptom severity index, depression, & anxiety, so as to determine: a) the relative effectiveness of these therapies; and b) the characteristics of patient responders and non-responders to each therapy.

Hypothesis 1. Patients randomized to the reflexology group will have lower fatigue severity, summed symptom severity index, depression and anxiety at weeks 1-4, as compared to those randomized to meditative practices.

Aim 2. Among patients who do not respond to reflexology with lowered fatigue severity during the first intervention stage, to determine the value added by meditative practices during weeks 5-8 (2nd intervention stage) vs continuing with reflexology alone for managing the fatigue severity and the 3 secondary symptom outcomes: summed severity index, depression, and anxiety.

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

Aim 3. Among patients who do not respond to meditative practices with lowered fatigue severity during the first intervention stage, to determine the value added by introducing reflexology during weeks 5-8 (2nd intervention stage) vs continuing with meditative practices alone for managing fatigue severity and the 3 secondary symptom outcomes: summed severity index, depression and anxiety.

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

Aim 4. To compare improvements in fatigue severity and the 3 secondary symptom outcomes among three groups created by the first randomization.

Hypothesis 4: Patients randomized to the respective intervention sequences will report lower fatigue severity and improvement on 3 secondary outcomes: summed symptom severity index at weeks 1-8 and week 12, depression and anxiety at week 12 compared to controls.

Aim 5. To explore which dyadic characteristics observed during the first intervention stage are associated with optimal patient symptom outcomes during the 2nd intervention stage (weeks 5-8)

and follow-up at week 12, so as to determine tailoring variables for the decision rules of sequencing future intervention stages.

Sample

Patients are approached at the participating oncology clinics that include two comprehensive cancer centers and three community oncology settings. 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) presence of deep vein thrombosis or painful foot neuropathy.

Solid tumors were selected because fatigue is prevalent during their treatment (Sikorskii, Given, Given, Jeon, Decker, Decker, et al., 2007; Sikorskii, Given, You, Jeon, & Given, 2009b; Wyatt, Sikorskii, Rahbar, Victorson, & You, 2012). Emerging evidence supports the potential efficacy of reflexology and meditative practices for fatigue management (Haller et al., 2017; Lehto, Wyatt, Sikorskii, Tesnjak, & Kaufman, 2015; Wyatt, Sikorskii, Rahbar, Victorson, & You, 2012; Wyatt et al., 2017). The cut-off of ≥ 3 indicates a moderate level of fatigue based on established interference-based cut-points (Given, et al., 2008). Virtually all patients with solid tumor cancer who are on chemotherapy will reach a threshold score of 2 or higher on fatigue at some point, and the cut-off score of 3 was found to be optimal in past work for balancing sensitivity and

specificity in predicting needs for future symptom management (Jeon, Given, Sikorskii, & Given, 2009).

A friend/family caregiver participates with each patient and completes a consent form. Caregiver inclusion criteria: 1) age 18 or older; 2) able to speak and understand English; 3) have access to a telephone; 4) able to hear normal conversation; and 5) willingness to be trained in reflexology and meditative practices.

Sample size

The sample size determination 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, the effect size of 0.45 was used, the smallest seen in preliminary work (source blinded for peer review) 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 resulted 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), 276 patients needed 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 symptom management

trials with solid tumor cancers, (Sikorskii, Given, Given, Jeon, Decker, & Decker, 2007; Wyatt et al., 2012) 430 patients will need to consent.

Participants are 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 to participate in the study, the recruiters seek consent to review their medical record for demographics and are asked the reason for refusal. These data contribute to external validity and generalizability of the findings.

Procedures

Recruitment. Recruiters at each site are trained by the study Education Coordinator; they have only research roles and do not provide direct patient care. They 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 follow up during a clinic visit or by phone to further explain the study, answer questions, and to discuss the study with caregivers. If verbal consent is obtained over the phone for the patient and/or caregiver, the consent forms in the packet are signed and returned in the stamped envelope provided.

Randomization. Following the baseline interview, dyads are randomized to either reflexology, meditative practices or to the standard care control groups. Randomization is completed using a computer minimization algorithm (Taves, 1974) that balances arms by recruitment location, patient's site of cancer (breast, lung, colon, prostate, other), stage of cancer (early versus late), and type of treatment (hormonal therapy alone versus chemotherapy or targeted therapy with or without hormonal therapy). The second randomization occurs for those dyads where patients do not respond on fatigue after the first 4 weeks of therapy. The second randomization is

implemented using the same approach as the first, with the same balancing factors, except that the randomization allocates dyads into 2 groups: continuing the same therapy or adding the other one during weeks 5-8.

Interventions. 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 (Watson & Voner, 2008). 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 (Watson & Voner, 2008).

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 (Kabat-Zinn, 2009). 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 (Arch & Craske, 2006; Branstrom, Kvillemo, Brandberg, & Moskowitz, 2010; Carlson, Speca, Patel, & Goodey, 2004; Shapiro, Carlson, Astin, & Freedman, 2006; Tacon, Caldera, & Ronaghan, 2004).

Caregivers are trained by either a study reflexologist if a dyad is randomized to reflexology. For dyads randomized to meditative practices, both patient and caregiver are trained by a study meditation provider. After 4 weeks of delivering the therapy, training in the second therapy occurs according to re-randomization. The dyads can select the day of the week for each therapy when randomized to both during weeks 5-8. Caregivers 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 study procedures. The number of additional sessions

per week is not restricted in a home-based intervention, and the number of sessions delivered is tracked weekly. Patients are also called weekly to inquire about completed intervention sessions and their symptoms.

The intervention trainers teach the study providers who work directly with patients and caregivers. Study reflexology providers are practicing reflexologists, who are trained in the specific study procedural steps. Study meditation providers are health professionals with formal meditation training. Training for both therapies includes didactic information, written procedural steps, role-playing, demonstrations, and return-demonstrations based on our study-specific criteria. All study providers must demonstrate procedural proficiency $\geq 90\%$ to begin and continue (quality assurance (QA) checks) with participants. Both therapies have written instructions with diagrams that are left with caregivers. Each study provider is 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 resolve any errors.

Intervention fidelity. Intervention fidelity is assured through established methods outlined by the NIH Treatment Fidelity Workgroup on consistency in dose, providers, delivery, receipt and enactment of the intervention (Bellg et al., 2004). Lead study trainers for reflexology and meditative practices providers assure fidelity through maintenance of the procedural steps and delivery. *Dose Consistency.* Initially all patients randomized to intervention groups have four weeks of either reflexology or meditative practices with their caregiver. Weekly sessions for each of the two therapies are approximately 45-60 minutes long. *Provider Consistency.* All study providers pass a demonstration of $\geq 90\%$ proficiency as judged by the lead trainers' score on the checklist for both therapies before beginning with caregivers. Caregivers must also achieve 90% accuracy. *Delivery Consistency.* There is a quality assurance (QA) check and booster session

conducted biannually for each study provider (those who teach caregivers one or both therapies), with a 90% proficiency required 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 Educational Coordinator calls every seven days to ask the number of completed sessions since the last weekly call. A minimum of 1 session is required, with the exact number of sessions reported by the caregiver recorded weekly. Thus, fidelity of the receipt and enactment of each therapy is documented weekly over the 8-week intervention period.

All participants are mailed a thank-you letter with a local complementary therapy directory enclosed after the week 12 data collection. Control caregivers are offered a complimentary training session of their choice (reflexology or meditative practices).

Data Collection

Interviews. All patients and caregivers in intervention and control groups have data collected twice via telephone interviews: baseline and study week 12 to capture post-intervention effects. Interviewers are blinded to dyad's group assignment.

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

Weekly Calls to Patients. The Education Coordinators make the weekly calls to all patients to assess symptoms during the 8-week intervention period or an equivalent time frame for the

control group. Therefore, the attention of asking patients about their symptoms is equalized across groups. When a symptom is rated at a 7 or higher on the 0-10 scale, patients are asked to contact their oncology office. For patients randomized to reflexology or meditative practices, data on the number of completed sessions are collected during these calls. Also, weeks 1-4 call data are used to assess response on fatigue (see definition of symptom response below).

Weekly calls to Caregivers. The Education Coordinator calls the intervention caregiver every 7 days to assess the number of sessions conducted with the patient since the last call 7 days ago. During weeks 5-8, if re-randomized to add another therapy, the number of sessions is recorded for the initial and added therapy. The Education Coordinator makes these calls because interviewers need to be blinded to dyad group assignments.

Measures

Study measures have published evidence of reliability and validity with samples of patients with cancer and informal cancer caregivers. The interviews take 30-45 minutes.

Primary Symptom Outcome - Fatigue

Brief Fatigue Inventory (BFI) (Patients; baseline & week 12) (Mendoza et al., 1999). Physical and emotional components of fatigue are measured with the Brief Fatigue Inventory for efficient assessment of fatigue severity and interference with daily life. The instrument consists of nine items. The first three items ask respondents to rate their fatigue severity “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.

Attentional Function Index (AFI) (Patients; baseline & week 12) (Cimprich, 2010). The cognitive component of fatigue is 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 (Cimprich, 1992, 2010). In previous studies with lung cancer, alpha reliabilities were .89 and .91 respectively (Lehto, 2013).

Measures of Secondary Symptom Outcomes.

Symptom Inventory (Patients; baseline & week 12 & weekly calls) (Cleeland, 2007). 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 (Cleeland et al., 2000). It has been recently updated to include the most common symptoms experienced by patients undergoing modern cancer treatments (Cleeland et al., 2013b). 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 above) is used as a secondary outcome in study Aims 1-4 and in building optimal decision rules in exploratory Aim 5. However, during weekly calls to patients, the 19-symptom expanded MDASI (and not BFI or AFI) is used to efficiently collect symptom data; the fatigue item from the MDASI is used for the determination of responders after week 4 due to the established cut-points with this measure. The

available cut-points for mild, moderate, and severe fatigue needed for response determination are based on a single item fatigue rating (Given et al., 2008; Mendoza et al., 1999; Wang et al., 2014) (see determination of response below). Also in consideration of the patient, administration of the longer BFI would substantially increase respondent burden during 12 weekly calls.

Measures of Secondary Outcomes of Depression and Anxiety. PROMIS-short forms 4: depression and anxiety (Patients; baseline and week 12) (Cella et al., 2010; PROMIS, 2012, 2013a, 2013b). These two symptoms are not directly covered by MDASI, which includes related items of distress and sadness. Therefore, the additional PROMIS measures for these symptoms are included (Cella et al., 2010; Cella, Yount, & Rothrock, 2007). Testing in more than 21,000 individuals from the United States 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. The 4-item short forms were chosen to minimize respondent burden while maintaining measurement precision.

Determination of Response on Fatigue during Weeks 1-4 for the Purpose of Randomization (*Patient; weekly calls*). As mentioned previously, fatigue response is assessed with the fatigue item score from the MDASI administered in weekly calls. First, symptom onset is defined 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. (Given et al., 2008). 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. A cut-off score of 3 or higher based on the

inclusion criteria means that at intake patients are experiencing fatigue at a moderate or severe level. Patients who started with a severe level of fatigue at onset and ended with moderate or mild levels by the 4-week observation, and patients who started at a moderate level and ended at mild, are called responders on fatigue (Sikorskii, Given, You, Jeon, & Given, 2009a). Since responders demonstrate a substantial improvement anchored to fatigue interference with daily life after 4 weeks, they continue with the intervention for another 4 weeks. Patients who remain at moderate levels or move to severe at week 4 are classified as non-responders (Sikorskii et al., 2009a). These patients are 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.

Measures of Dyad Characteristics (Potential Covariates)

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

Chronic Conditions (Patients; baseline). The Bayliss tool is used to query the presence of 20 comorbidities. Patients can add co-morbid conditions that are not listed (Bayliss, Ellis, & Steiner, 2009).

Medical Treatment (Patients; eligibility & week 12). Chart data include anti-cancer treatments such as 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 are collected on side effects and toxicities including anemia and neutropenia.

Complementary Therapy Expectancy Scale (intervention group dyads during weekly calls)

(Devilly & Borkovec, 2000). This tool incorporates items that assess perceived thoughts and feelings related to complementary therapy use. It has been modified to ask about the current therapy or therapies the dyad has been randomized to.

Complementary Therapy Utilization (Patients; baseline & week 12) (Wyatt, 1993). Assesses the use of 24 therapies.

Caregiver Reaction Assessment Tool (Caregiver; baseline and week 12) (Given et al., 1992).

Caregiver burden is 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.

PROMIS Profile-29 (Caregivers; baseline & week 12) (Cella et al., 2010; PROMIS, 2010). 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 the studied interventions are delivered by or practiced with the caregivers, caregiver health may influence the decision rules explored in Aim 5.

Patient Satisfaction with Friend or Family Caregiver Involvement. (Patients; week 12) (Wyatt & Frambes, 2012). This survey consists of 5 items that query patient satisfaction with their caregiver involvement. Since the survey is unique for the purposes of this study, it has not been validated with other samples previously. Formal psychometric evaluation is planned during forthcoming analysis of the trial data.

Protocol Integrity Assessments

Therapy protocol adherence is evaluated by the number of completed sessions per week.

Attrition dates and reasons are documented including factors such as being unable to reach the patient or the patient stating she/he wishes to discontinue. Training Forms for proficiency of reflexology and meditative practices trainers are completed at each training and annual refreshers by the lead providers. Study providers also use the proficiency checklist when training caregivers at weeks 1 & 2 and if a second therapy is added at weeks 5 & 6.

Analytic Methods

All data are entered into the secure web-based database. To maintain security, data are stored within a server different from the server of web application. Quarterly quality assurance checks of the data are performed. De-identified data will be transferred into SAS 9.4 for analyses.

Baseline Comparisons and Regression Techniques. The distributions of outcomes at baseline and potential covariates will be summarized. Outliers will be investigated by inspecting the residuals, and models described below will be fit with and without outliers to examine their influence on the results.

Attrition Analyses and Handling of Missing Data. Dyadic characteristics will be compared for 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. To inform the generalizability of findings, characteristics will also be compared for those who completed the study with those who did not within their designated group. The regression techniques described below allow for missing at random (MAR) mechanisms (Little & Rubin, 1987). 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) (Hogan, Roy, & Korkontzelou, 2004; Shen & Weissfeld, 2005). Since NMAR or MAR assumptions are not directly testable, sensitivity analyses will be employed to investigate the robustness of the results under pattern-mixture or other models.

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

Aim 1, Hypothesis 1 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 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. Primary interest is 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 .

For Aim 1, part b), patients who are responders or non-responders 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. 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. 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 two secondary outcomes will come from the significance of the coefficient for group assignment in the second randomization.

Aim 3, Hypothesis 3. 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. 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 the 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 the randomization.

Exploratory Analysis: Aim 5. 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 that were 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 (Moodie, Richardson, & Stephens, 2007; Robbins, 2004). 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 fatigue severity, summed severity of other symptoms, depression and anxiety, and the optimal decision rule will be found using backward induction by maximizing these functions (Murphy, 2005; Sutton & Barto, 1998). Given 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 ("PROC QLEARN (Version 1.0) ", 2012) developed by Murphy and colleagues (Murphy, 2003). 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, tailoring variables will be

identified 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.

Human subjects

Institutional Review Board (IRB) approval was obtained at investigators' University and participating sites.

Security Procedures for Transfer, Implementation, and Storage of Data. All computers used to collect and send data during implementation of the study or to receive or store data at the central location are password-protected and have appropriate firewalls and security protections. Transfer of protocol data occurs by the password-protected server. Paper copies of all consent forms are transmitted via secure fax and are retained in locked files.

Identification of Adverse Effects: Adverse effects are monitored by both the interviewers and Education Coordinator who telephone participants, and the reflexology or meditative practices providers who interact with the dyads during training in the respective therapy. All adverse events are reported to the Project Manager within 24 hours, who notifies the investigators. The investigators evaluate the adverse event, and if they decide it is moderate or serious, they convene Data and Safety Monitoring Committee. All events determined to be serious by the committee will be reported to the University IRB and the NIH project officer within 48 hours. The study is low-risk; therefore, serious adverse events are not anticipated.

Data Safety & Monitoring Committee: The investigators' College has implemented a Research Quality Assurance (RQA) Group comprising the Associate Dean for Research, the Research Center Coordinator, a senior-level researcher, and a statistician to oversee studies conducted by faculty. The group reviews any changes needed to the study protocol or conflict of interest

issues. The investigative team reports to the RQA committee include the summary of cumulative accrual by site; randomization; cumulative attrition; attrition by site, study group, and race/ethnicity; adverse events and serious adverse events; data completeness and quality; and a study Consolidated Standards for Reporting Trials (CONSORT) chart.

Discussion

To date, the study has enrolled 150 out of 430 dyads in one year of recruitment, with three years remaining. One of the challenges encountered during recruitment is the increasing availability of integrative oncology services that include reflexology or meditative practices at participating sites, making participants engaged in these therapies ineligible for the trial. While the availability of such services helps improve patient care, these services often require travel to the clinic where they are offered. In contrast, this study offers reflexology and/or meditative practices in the patients' homes.

Also, recruitment of participants consisting of patient-caregiver dyads is more challenging than individual recruitment. The recruiters approach patients in the clinic, and often the friend or family caregiver is not present with the patient. Many patients either do not have a caregiver, or do not want to ask their caregiver to participate with them, due to perceived additional burden over what the caregiver is already doing for the patient. The team draws on past experience in addressing this issue (Holmstrom, 2015). Once a contact with the caregiver is made, the refusal rate is low, and the caregivers agree to participate to increase their meaningful involvement in patient care. Researchers planning to enroll patient-caregiver dyads may think of ways to approach the caregiver not only through the patient, but also through other avenues.

At least two of the four weekly contacts during weeks 1-4 are required for the determination of symptom response as a criterion for re-randomization, yet some patients skip some of the weeks.

For those with one available weekly symptom assessment, severity of fatigue from the baseline interview is used as an additional needed time point in response determination. Those who do not complete any of the weekly calls during weeks 1-4 are considered drop-outs, and the sample size of 430 allows for 23% attrition in order to maintain sufficient power to test study hypotheses. To date, 40 dyads have been re-randomized. The rate of response of 20% was used for planning purposes in the sample determination. Currently, the response rate is somewhat greater for both therapies (33% for reflexology, and 24% for meditative practices). If this trend continues, the study may need to recruit more participants to have sufficient power to test Hypotheses 2 and 3 that involve non-responders to the first stage. Therefore in planning of future trials, using the most optimistic estimate for response rate would produce the most conservative sample size requirement.

Patients of all cancer stages are eligible for the study if they are receiving treatment at intake, and disease progression after consent does not preclude continued participation. In the team's past studies with late stage breast cancer patients (source blinded for peer review), many patients continued to participate even if they decided to stop treatment due to disease progression.

Also, the team's extensive past experience with two therapies, reflexology and meditative practices (source blinded for peer review), ensures that caregivers are successfully trained in these therapies, and fidelity is maintained. The fidelity scorecard (source blinded for peer review) allows for quantitative evaluation of fidelity of caregiver-delivered reflexology intervention. Similar tools can be developed for other therapies to support scientific rigor and reproducibility of study results.

In summary, the SMART design advances intervention science by optimizing individualized patient care for the best possible outcomes. This design leads to decision rules for personalized

symptom management that are consistent with precision medicine. Once tested in a future confirmatory trial, these decision rules allow clinicians to implement the most useful therapy for patients possessing the characteristics that can reap the greatest benefit.

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