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Intervention Fidelity: Aspects of Complementary and Alternative Medicine (CAM) Research

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Abstract

Background—The Treatment Fidelity Workgroup (TFW) established by the National Institutes of Health (NIH) provides a 5-point structure for intervention fidelity: dosing, interventionists' consistency, intervention delivery, receipt and enactment of the intervention. Using our reflexology trial, we apply the first three points.

Objectives—Study objectives are to: 1) evaluate key dosage dimensions associated with CAM research; 2) evaluate approaches to interventionists' consistency of delivery of CAM protocols; and 3) evaluate and discuss data that reflect CAM intervention fidelity.

Intervention—Women with late stage breast cancer (N=318) were randomly assigned to either 4 weeks of reflexology, placebo, or standard care.

Results—Dosing consists of three dimensions: frequency (4-sessions), duration (30 minutes), and interval between sessions (5–9 days). Interventionist consistency revealed over a 90% accuracy rate in following the protocol; 84% and 89% completion rate of the 4 session in the reflexology and placebo groups respectively; and no differences in attrition after randomization between reflexology and placebo groups (17% and 15%, respectively). Intervention delivery, examined through debriefing data, indicated a significantly higher rate of correct guesses on group assignment in the reflexology group as compared to the placebo (82% versus 46%, p-value=. 0002).

Conclusions—This study points out the relevance of dosing, interventionists' consistency, and delivery data within a CAM clinical trial, as well as the challenges of blinding.

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Implications—Monitoring intervention fidelity by using the key areas identified by the BCC ensures that findings from a clinical trial are meaningful and have the potential to be translated to clinical practice.

Introduction

Breast cancer is widespread among women in the western world,[1, 2] and the second cause of cancer mortality among women. Women with breast cancer are one of the most likely groups of patients to seek supportive care for symptom relief and health-related quality of life (HRQOL) enhancement during treatment.[3, 4] According to Boon and colleagues[5], over 80% of women with breast cancer use complementary and alternative medicine (CAM) for these purposes. Other investigators have also reported high rates of CAM use among women with breast cancer and other cancer populations.[6, 7]

CAM interventions have gained widespread acceptance, largely without the clinical evidence for safety and efficacy. Such evidence is expected for conventional medicine,[4, 8] and the National Center for Complementary and Alternative Medicine (NCCAM) takes the position that CAM therapies should be investigated with the same rigor as conventional treatments and held to the same standards of safety and efficacy.[9] The randomized clinical trial (RCT) continues to be the gold standard for research by which health professionals make clinical decisions.[10, 11] However, not all RCTs of CAM interventions are well-designed and methodologically sound.[8, 12] A systematic review of 44 CAM studies with cancer patient-reported outcomes associated with health-related quality of life HRQOL, revealed that only 16 studies (36%) could be classified as being robust enough to contribute to clinical decision making.[13]

Researchers from the National Cancer Institute (NCI) analyzed the content of 46 proposals submitted by investigators in the Community Clinical Oncology Program (CCOP) to their Office of Cancer Complementary and Alternative Medicine. According to Buchanan et al. (2005),[12] measurement and design issues were common among the proposals evaluated. In addition, standardization and quality control procedures for the intervention were frequently deficient. Applicants often failed to identify an appropriate timeline for assessments during the course of the studies, and a recurring limitation was the lack of an appropriate comparison group.[12]

Key elements of strong research designs used to rigorously evaluate CAM interventions are directly associated with intervention fidelity.[8, 10, 12, 14, 15] Procedures that maintain fidelity through preserving internal validity are critical to enhancing external validity for the accurate translation of findings to practice.[16] Radziewicz et al., defined intervention fidelity as, “The adherent and competent delivery of an intervention by the interventionist as set forth in the research plan.” [17(p. 194)] In other words, intervention fidelity means the consistency and integrity with which the intervention is delivered by the study interveners. Five areas of fidelity were put forth by the Treatment Fidelity Workgroup (TFW) of the National Institutes of Health (NIH) Behavior Change Consortium in 1999. The five areas provide an infrastructure to foster fidelity within projects and strengthen the application of evidence-based practice, and include intervention dose, training interveners, delivery of intervention, receipt of intervention, and enactment of intervention skills.[16] While our exemplar study does not include a behavior change that would incorporate the final two areas of the TFW recommendations, we do find the first three areas that relate to intervention delivery, relevant and valuable to our discussion. Using our current NIH reflexology RCT[18] as an exemplar, we frame the topic of intervention fidelity around the three areas of successfully implementing intervention delivery: (a) intervention dose, (b) intervener training, and (c) intervention delivery. Reflexology is a method of using thumb

pressure with a walking motion on reflex areas of the feet which correspond to the glands, organs, and systems of the body.[19] The following research objectives are addressed:

1. Evaluate key dosage dimensions associated with CAM research.
2. Evaluate approaches to interventionists' consistency of delivery of CAM protocols.
3. Evaluate and discuss data that reflect CAM intervention fidelity.

Study Background

When completed, the exemplar study of reflexology will include 435 women with advanced breast cancer. To date, 364 women have consented to participate in the study. The reflexology trial has a three-group design: women are randomized to (a) reflexology, (b) placebo, or (c) standard care control group. The two active groups of the study receive four consecutive weekly sessions of either reflexology or placebo sessions. Placebo sessions involve foot manipulations of the same length as reflexology sessions that are dosed at 30 minutes per session (15 minutes to each foot). The control group continues with standard care, as do women in the two active groups. Standard care for all enrolled patients includes conventional medical care. Longitudinal outcome data are gathered at three time points for all three groups. In addition, for the two active groups, data capturing the delivery of reflexology or placebo sessions are recorded following each session.

Study Sample

The sample for this paper consists of the 222 women who completed the baseline interview and received the current protocol in the exemplar study (see Table 1 for demographics). The study inclusion criteria are: (a) female; (b) age 21 years or older; (c) diagnosis of Stage III or IV breast cancer, or metastatic or recurrent breast cancer; (d) able to perform basic activities of daily living; (e) free of a diagnosis of mental illness on the medical chart; (f) able to speak and understand English; (g) having access to a telephone; (h) undergoing chemotherapy and/or hormonal therapy for breast cancer at intake to the study; (i) Palliative Prognostic Score of 11 or lower (i.e., a 30 day survival probability of ≥70%);[20] and (j) oriented to all three cognitive spheres. Exclusion criteria are (a) receiving an investigational chemotherapy drug; (b) receiving hospice care at intake; (c) living in an extended care facility; (d) bedridden; (e) undergoing bone marrow transplant; (f) regularly using either reflexology, foot massage, or pedicure with foot massage.

Recruitment Procedures

Patients are recruited from 14 hospital-affiliated cancer clinics throughout the Midwest. Recruiters from each site identify eligible patients through discussion of patients at internal grand rounds and medical chart reviews, approach individual patients to describe the protocol, and answer any of their questions. The education coordinator of the study trains each recruiter according to the established protocol for the study. This ensures that the recruitment protocol is consistently followed across sites. The Institutional Review Boards of the investigators' university and of each clinical site have approved the study.

Following recruitment and consent, patients are interviewed at baseline via the telephone. Randomization is performed following the baseline telephone interview using the minimization procedure proposed by Taves[21] and implemented in SAS.[22]

Measures

While this paper is focused on study processes related to intervention fidelity, it is also useful to be aware of the outcome measures. In the parent study, the principal sources of data are three telephone interviews obtained at baseline prior to the intervention (Wave 1), immediately after the intervention which is week seven of the trial (Wave 2), and again 6 weeks later which is week 13 of the trial (Wave 3) and based on the recommendation of the certified reflexologist's experience with cancer patients. Primary endpoint outcome indicators are assessed at each data collection point by use of the Functional Assessment of Cancer Therapy-Breast (FACT-B) Scale- Version 4,[23] and the Long-Term QOL (LTQL) Spirituality Subscale.[24] Intermediate physical indicators are assessed at each data collection point by use of the SF-36; [25] the Physical Symptom Experience; [26] the Brief Fatigue Inventory; [27] and the Brief Pain Inventory-Short Form.[28] Intermediate emotional indicators are assessed at each data collection point by use of the State Anxiety [29] and the Center for Epidemiologic Studies Depression Scale (CES-D).[30]

Clinical measures are assessed by medical chart audit and include co-morbid conditions, cancer-specific procedures, treatment-related complications, pharmaceuticals, transfusions, and chemotherapy corresponding with each data collection point. Patients' use of CAM is assessed using the CAM Utilization Instrument.[31] This instrument assesses respondents' use of 24 CAM therapies including frequency of use. Finally, a debriefing measure assesses reflexology and placebo group participant's opinion regarding their allocation to the reflexology or placebo treatment group at the end of the third and final telephone interview. Results from the analyses of outcome data on efficacy are forthcoming once the parent study is completed.

For this paper, intervention fidelity is evaluated through four data sources. We use records from protocol training for interveners, protocol delivery data collected following each reflexology or placebo session, attrition data, and debriefing data on group allocation (as mentioned above).

Conceptual Model

The conceptual model guiding the intervention fidelity of this study is depicted in Figure 1. At the far left, study participants are described by demographic variables. Next, the three study groups are identified as reflexology, placebo, and control. The fidelity markers indicate the measures taken to assure intervention fidelity, and are the focus of this paper. Finally, the primary and intermediate study outcomes of the parent study are represented on the far right of the model.

While the reflexology study is serving as an exemplar in this model, the model could be applied broadly to other CAM interventions. There are five categories of CAM categories established by NCCAM: Mind-body, manipulative and body based, biologically-based, energy therapies, and alternative medical systems.[9] The reflexology study falls within the Manipulative and body based Category. This category includes the hands-on therapies such as massage or reflexology, and body focused therapies like yoga.

Intervention Fidelity Research Objectives

Research Objective One

Evaluate key dosage dimensions associated with CAM research. The first area of intervention fidelity recommended by the TFW is dosage which is central to study design. According to Calsyn[32] dosage is the amount and type of prescribed treatment received by each participant in the experimental and comparison groups. For CAM therapy such as

reflexology, dose consists of frequency (number of sessions), duration (minutes of each session), and interval (amount of time between sessions).[16] Because few CAM therapies have been subjected to rigorous scrutiny, the optimal dose is frequently unknown.[33] Therefore, the first step in formally evaluating a CAM therapy is determining how much to give, how often, and at what interval. This determination can be accomplished through pilot work such as the preliminary work we conducted prior to the exemplar study used here to highlight the areas of fidelity,[34, 35] a review of data-based literature, and expert opinion.

Frequency - Number of Sessions—According to Ezzo[33] protocols for hands-on CAM therapies in clinical trials should be based on preliminary studies which establish the minimally effective active dose. One source of information on frequency for our exemplar study came from pilot work conducted with 27 breast cancer patients who were undergoing chemotherapy at one of our Midwest oncology clinics.[36] Results from our pilot where 5 sessions were used, demonstrated positive trends after 3 sessions of reflexology on our primary outcome of QOL.

The second source of information can be derived from data-based reviews such as Cochrane publications. This literature is useful in conducting an evaluation of the well-designed studies of the therapy to be tested. Further, a review of studies that used similar measures to those of the primary outcome of the planned study may contribute to dose decisions.[37] In many studies, only one CAM session is used; others used multiple sessions, where the range of sessions needs to be evaluated.[38–42] Therefore, it is also pertinent to look at studies that indicated a positive cumulative effect when multiple session are used.[40, 43] Available literature for the reflexology study was sparse. At the time the exemplar study was designed, there were two cancer-based RCT studies available on reflexology to draw upon.[44] One study administered 1 session,[45] and the other used 3 sessions delivered on days 1, 3, and 5 of hospitalization for 40 minutes each.[44]

The third source of information for dose in the exemplar study was based on the opinion of the expert reflexologist with 25 years of experience, and based on her certification the Ingham Reflexology method.[19] She believed that 4 sessions would more closely assure the desired health benefits to be noted.

Compiling information from the preliminary work, data-based literature, and expert opinion, we selected 4 sessions for the reflexology RCT. We felt this was a reasonable number of sessions to detect a therapeutic effect. Five weeks are allowed to accomplish the 4 sessions in order to accommodate any scheduling conflicts. Based on positive trend in our pilot with 3 sessions, it was determined that for analysis purposes, 3 sessions would constitute a completed protocol. Every effort is made to attain the 4 sessions for each participant, and no one receives 5 sessions even though the 5-week window is built into the design.

Duration - Minutes of Each Session—The same three sources of information can be used to determine the length of each session, i.e., pilot work, literature, and expert opinion.[40, 46–49] In addition, the length of sessions needs to be compatible with the clinical setting where the intervention will be implemented. Interviews with nurse leaders in the clinic may be critical to balancing the therapeutic effect time with practical issues. There may also be a national or international organization associated with the intervention that can contribute duration information.[19] In our pilot work, 30 minutes (15 minutes for each foot) was adequate to cover all the necessary reflexes and was clinically acceptable. For our reflexology study, the two available oncology studies in the literature ranged from 20 minutes to 40 minutes.[44, 45] Our reflexology expert indicated that a typical session would be 60 minutes since clients assume a one hour therapy for most community-based CAM. However, once she determined how much time was needed for each reflex in the protocol,

she agreed that this could be accomplished in 30 minutes. Considerable emphasis was given to clinical appropriateness (i.e., amount of reflexologist time spent with patients that did not interfere with medical treatments), and the fact that trends were observed with 30 minutes in our pilot. We acknowledge that our RCT is helping establish the therapeutic duration.

Interval - Amount of Time Between Sessions—This dimension addresses the interval between sessions, which typically ranges from days to weeks. A session may also be done before, after, or during a medical treatment such as chemotherapy. In other cases, the interval between sessions may run parallel with a specific medical therapy such as radiation therapy (RT). In another one of our studies, patients who receive six weeks of RT also receive our CAM therapy to match this same time frame in order to provide supportive care during the potentially distressing side effects of RT.[50] Considering the literature, Hodgson[44] intervened with reflexology on days one, three, and five of the study to deliver the three sessions in an in-patient setting; whereas, Stephenson[45] used only one in-patient session. In our pilot, we demonstrated positive trends in outcomes with weekly sessions that were most practical for our out-patient sample. Our expert reflexologist also recommended weekly sessions.

Based on the available information, we again selected weekly sessions for the RCT. Further, a range of 5 to 9 days was permitted in order to provide a window of two days on either side of the standard 7 day interval. The range was based the patient satisfaction item in the debriefing tool of the pilot, and allowed for scheduling options for both the patient and the intervener.

Overall, when considering the three parameters of dose, it is best to keep the selected dose at the high end of concentration for frequency, duration, and interval. This will help guard against missing a beneficial effect due to inadequate dosing. If there are multiple sessions to the intervention, these can be scheduled at the initial contact so that the participants can write them in their personal calendar as a reminder. The study office can also make reminder calls the day before the next scheduled session, so as to increase compliance with the study dose. Finally, it is critical to assess the use of any other CAM therapies during the clinical trial for both the active and placebo groups. Any similar or related CAM therapies participants receive during the intervention are not part of the intended intervention or placebo and can artificially inflate the treatment effects.[32] Spending time on this process can help prevent attrition, missed sessions, and inflated effects, all of which are essential to intervention fidelity.

Research Objective Two

Evaluate approaches to interventionists' consistency of delivery of CAM protocols.

The second area of fidelity outlined by the TFW focused on the interveners who deliver the study intervention and are essential to any RCT with multiple groups and types of interveners. The groups may or may not include a standard care and a placebo group, but the active intervention group is always essential. Whatever the number of groups in the design may be, the consistency of protocol delivery within any given group is critical. Calsyn[32] cautions against intervention diffusion. This can occur when the same personnel are used to intervene with both the experimental and comparison groups.

According to Berman and Straus,[8] the best way to answer questions about the safety and efficacy of an intervention in a given patient population is to use a placebo-controlled study. However, many CAM studies have compared only an intervention group to a standard care group.[10, 33] Buchanan et al. [12] identified a stronger design using three groups, i.e., experimental, placebo, and a standard care control group. Once a three-group study is

selected, the challenge becomes how best to design the placebo protocol. This challenge brings forth issues that involve all three groups, including the interveners in both the active and placebo groups. Both sets of interveners (one for reflexology and one for placebo) need to follow a specific protocol, be selected carefully by the research team, and take into account seemingly harmless extraneous factors such as social interaction.

Standard Care Control Group—The standard care group enables researchers to control for the natural progression of the disease.[33] While no interveners are needed for this group within the design, it still contributes important information to the overall study. Researchers can estimate the nonspecific effects of social interaction and sometimes touch in the placebo group through comparison with the standard care group. Further, the standard care group can help control for other contributors to the placebo effect, including regression to the mean, patient use of concurrent therapies, and the influence of the study itself, or the Hawthorne effect.[10] Through analysis, the three-group design enables the researchers to sequence the specific aims of the study. Thus, in the final analysis it is possible to compare the intervention group to the placebo group, the intervention group to the control group, and the placebo group to the control group.

Active Experimental Group—Berman and Straus[8] state that CAM therapies can be difficult to administer in a standardized format that is reproducible across interveners. Interveners have a tendency to individualize treatments for each patient based upon their clinical judgment. Intervener skills, experience, and empathy may also complicate efforts to isolate and measure the “active ingredient” of the therapy being tested.[51] The experimental group of a CAM therapy trial must isolate the “active ingredient” of the therapy being tested and be certain the interveners deliver it consistently. For example, in the exemplar reflexology study, the “active ingredient” is the walking thumb pressure over specific foot reflexes.

Critics of the RCT argue that patients frequently use CAM therapies in combinations, or “bundled,” rather than in isolation.[51] Some previous CAM studies have attempted to test combinations of therapies offered either as bundles or by patient preference.[51, 52] The inherent problem in research of bundled therapies is the inability of the investigators to isolate the active ingredient that makes any single therapy efficacious.[8, 10] The active ingredient must clearly be only a part of the experimental group, that is delivered by the interveners.

Placebo Group—The strongest design is when a placebo control group is incorporated into CAM research to show that any change in the outcome variable is caused by the active ingredient of the CAM therapy being tested, rather than other factors such as physical touch or social interaction. Placebo group issues plague research of physical modalities, whether in conventional medical modes such as physical therapy or CAM therapies such as massage and reflexology.[10, 12, 33] Richardson[53] suggests that the placebo intervention should mimic the experimental intervention without containing the “active agent” likely to bring about a change in the outcome variable. This is the challenge of creating a placebo intervention for a CAM trial. The placebo intervention must appear similar to the experimental intervention, interact with the same body part (when physical touch is involved), and take the same amount of time. While the placebo intervention must be pleasant enough to encourage compliance, it cannot contain the active ingredient that could serve as a change agent for the outcome variable.

In our exemplar reflexology study, we adjusted the placebo protocol because of a bleed-through effect between reflexology and placebo. We believed this effect was because the placebo foot manipulation targeted locations that were very close to the actual reflexology

points. Stimulation of the reflexes is hypothesized to be one of the active ingredients of reflexology. With multiple reflexes being located close to each other on the foot, avoiding one of the reflexes necessitated getting close to another reflex. Once this problem was observed, a second reflexologist reviewed the placebo protocol. The second reflexologist identified three foot locations used in the placebo protocol that were too close to the specific reflexes intended to be stimulated only in the reflexology protocol. In addition, the actual time spent stimulating the reflexes in the reflexology group was noted to be just short of the prescribed 15 minutes per foot. As a result of these findings we redesigned these aspects of the placebo protocol to completely avoid the therapeutic reflexes, and to ensure that the time of active stimulation of reflexes in the reflexology group was equal to 15 minutes per foot. This change necessitated noting participants who received the new versus the old placebo and reflexology protocols. At the end of the study, we will determine through analysis if there are different outcomes associated with each of these protocols.

Another complexity in designing placebo conditions for testing CAM therapies from the manipulative and body-based NCCAM category is dealing with therapeutic effects of placebo, which can be powerful and complex. When physical touch is involved, placebo may have a therapeutic effect. Multiple potential other sources of the placebo response are not clearly understood, and researchers believe that the placebo response can be influenced by cultural context, the therapist, the environment, and the power of patient beliefs and expectations.[53, 54] Specifically, Mehling et al.[10] suggested that it is necessary to control for therapist presence by equalizing attention, listening, and explanations across the intervention and placebo groups.

Patients are naturally alert to subtle indications of group assignment. Their expectations may greatly affect responses to active or placebo therapies. Blinding patients to their group assignment helps control for these differential expectations and for the potential bias in patient self-report outcome ratings.[10] Blinding of patients to their group assignment is vital to the study, and therefore the placebo intervention must be convincing.[33, 53] This requirement further complicates the design of placebo. In the case of the reflexology study, the placebo has to involve substantial human touch and foot manipulations, thus bringing up the other side of the placebo issue when the protocol too closely matches the active intervention and patients in the placebo group begin to benefit from these protocol components and demonstrate positive changes in outcomes.

Active and Placebo Group Intervener Considerations

There are several specific issues common to both the active and placebo interveners. They include following a clear protocol, careful selection of interveners by the investigators, and extraneous factors like social interaction and in some cases touch.

Intervener Protocol—A prescribed training manual, training tools, and objective criterion based evaluation are essential for both the active group interveners and the placebo group interveners.[55] In the exemplar reflexology study, the experimental protocol for the reflexology manual was developed by our expert reflexologist. Each reflexologist who participates in the study is trained by this expert using the established step-by-step protocol which specifies the timing and pressure over each reflex of the foot. Likewise, the placebo manual is used by the education coordinator who specifies the timing of the step-by-step procedure that mimics the true reflexology intervention without stimulating the foot reflexes or using the classic thumb walking motion. Training tools for both intervener groups include role playing with problem cases, demonstrations, and return demonstrations of the entire protocol. The education coordinator is responsible for oversight of scheduling the reflexologists with the active interveners and training for placebo interveners. All

interveners must match their established protocol criteria at 90% or higher before being assigned to their first patient.

Each intervener has a hard copy manual to refer to, which includes each step and the length of time to spend on each reflex (active intervener), and location on the foot (placebo intervener). Maintenance of the protocol fidelity is monitored for both the reflexologists and the placebo interveners quarterly through quality checks on their application of the protocol steps by the respective trainers. They must continue to agree with the protocol criteria at 90% or higher.

Intervener Selection—Intervener training is critical in order to minimize heterogeneity. According to Carroll et al.,[55] intervener heterogeneity in the delivery of an intervention can account for as much as 30% of outcome variance in clinical trials. However, Markowitz et al.[56] demonstrated that it was possible to reliably train interveners to deliver a specific intervention through use of a training manual.

There must be selection criteria for interveners, and a minimum amount of training or experience required. In the exemplar reflexology study, the reflexologist must have a specific amount of training in the Ingham Method of reflexology to qualify for the study. However, the placebo interveners are often more difficult to identify. They must be naive to reflexology but comfortable with physical touch of patients, so as to make the patient comfortable with the session. Physical touch is very powerful and impossible to control for with a hands-on placebo. We selected research aides, who were also nursing assistances at the various agencies, in order to provide a “caring stranger” who was at ease with touching patients. Nursing students can also be a good choice, but the selection of placebo interveners will vary depending on the therapy being tested.

Intervener Social Interaction—In the exemplar reflexology study, comparison of the reflexology group to the placebo group can be made for the nonspecific effects of social interaction. The training manual contains a scripted protocol of how to respond to various questions that the patients may ask. This standardizes the social interaction that is allowed in the sessions for both the reflexology and placebo groups. Interveners from both the reflexology group and the placebo group are trained not to initiate conversation once the session begins, but to suggest that patients relax, close their eyes, and concentrate on the experience of the foot session. The protocol includes acceptable topics to discuss when a participant persists with conversation. These topics include the weather and current events. All interveners are trained to portray a pleasant and professional demeanor. Interveners are never allowed to tell the participant their group assignment. Questions about cancer, the session, or cancer therapy are referred to the patient’s health care provider. Interveners are also cautioned not to mention sources of information on reflexology such as the Internet, television, or articles.

Research Objective Three

Evaluate and discuss data that reflect CAM intervention fidelity.

The third area of fidelity recommended by the TFW goes beyond interventionists’ data recorded during training and regular quality checks of the application of the protocol. These additional data reflect the delivery of the CAM intervention and include: (a) data provided by interveners after each session, (b) attrition data, and (c) participant debriefing data.

Intervener Data (see Figure 2)—In our reflexology study the intervener data includes any concerns around the foot area that prevent doing a session such as swelling or an open sore. Interveners also report whether there were any problems maintaining the minimal but

pleasant social interaction. The intervention encounter form (see Figure 3) allows us to keep track of completed sessions, their dates, and locations where sessions took place. These data are reviewed monthly, and any concerns are discussed at team meetings. Any high risk observations are reported to the project manager and principal investigator (PI) immediately. While this type of observation has not been reported during delivery of the first four years of the study, the PI would notify the patient's physician the same day.

Attrition Data (see Figure 2 and Table 2)—The second data source is tracked attrition from the study. It is important to know the drop out rates by study group, reasons for participants dropping out, and the timing of the attrition in relation to the intervention sessions. These data require a quantitative analysis comparing attrition rates and attrition reasons between reflexology and placebo groups. Any differences found would raise a question as to protocol fidelity. The most frequently encountered attrition reasons are listed and programmed in the database, thus a quantitative summary of frequencies of reasons is produced. In addition, a qualitative review of reasons (unique to specific patients and not included in the standard list of attrition reasons) is conducted in order to be certain there is not an issue with the delivery of the intervention or a specific intervener. In the exemplar study, the attrition rates following randomization are 17% in reflexology group and 12.5% in placebo group suggesting no concerns of patients dropping out because they recognized the placebo.

Further, the timing of attrition helps the investigators understand when it occurs in relation to a specific number of sessions of the therapy, or only after the full number of sessions is completed. This may have implications for the dose being too high, or the overall study being too long for a participant. These data should be reviewed on a regular basis to assure there are no issues specific to the intervention. In the exemplar reflexology study, we find that participants are unlikely to drop out during the weeks of the four reflexology and placebo sessions. In the reflexology group, 84% of patients completed all 4 protocol sessions, and the corresponding figure for placebo group is 89% (see Table 2).

Debriefing Data—The third data source is the debriefing data which occurs at the end of data collection. Participants are asked to guess if they were in the active or the placebo group of the study. If participants are able to guess their group assignment at a rate higher than a 50:50, the blinding of the intervention has been compromised at some point. In the exemplar reflexology study, the rate of correct guesses in the placebo group is 46%, and is not statistically different from 50%. However, in the reflexology group, the rate of correct guesses is 82%, which is significantly different from 50%, and from the rate of correct guesses in placebo group. These data suggested successful concealment of placebo but necessitated a review of the conduct of our reflexologists. No sources were found that could potentially identify a reflexologist, other than their level of professionalism.

Discussion

Maintaining and monitoring intervention fidelity within a CAM RCT has not received adequate research attention. The three dosing factors must be incorporated into the study design. When in doubt, it is better to err on the side of a higher dose to insure the proper detection of a therapeutic effect. Dosing information can be drawn from preliminary work, data-based literature, and expert practitioners in the specific CAM therapy. Protocol fidelity must be maintained throughout the study, which can be planned for ahead of time. Rigorous procedures must be in place to continually review the data collected by interveners and to re-check the interveners' accuracy in implementing the protocol on a regular basis. This involves adequate training of research study personnel and the development of tracking and monitoring systems. Although it is challenging to design placebo conditions that are

virtually identical to the treatment group yet don't include the "active ingredient", CAM studies that are able to successfully accomplish this will elevate the methodological rigor of this field and our knowledge of these therapies. Inclusion of a placebo group strengthens the evidence that it is the "active ingredient" accounting for the change in outcomes as opposed to extraneous elements such as social interaction or human touch. Finally, there are often sources for intervention delivery data, but they may be easily overlooked. We have found that intervener session data, attrition, and debriefing data provide additional information on intervention delivery. Each of the three areas outlined by the CDC for intervention delivery represents challenges to the investigator that must be discussed as a team and adhered to throughout the study.

Conclusion

According to the NCCAM and the NIH, both the widespread use of CAM and the amount of out-of-pocket spending on CAM by cancer patients provides rationale for critically evaluating CAM therapies.[57] CAM interventions have entered clinical use often without adequate trials of safety and efficacy.[8] If practitioners deliver CAM therapies or support patients in using such therapies, they need empirical evidence on safety and effectiveness.[58] In order for the results to be credible, intervention fidelity must be maintained throughout the study. According to Moncher and Prinz[59] fidelity is needed to ensure that fair, powerful and valid comparisons of replicable treatments can be made. Dissemination of accurate information to practitioners and to the public is only possible when CAM investigators incorporate the strategies best suited to testing each CAM therapy and maintaining intervention fidelity.[8]

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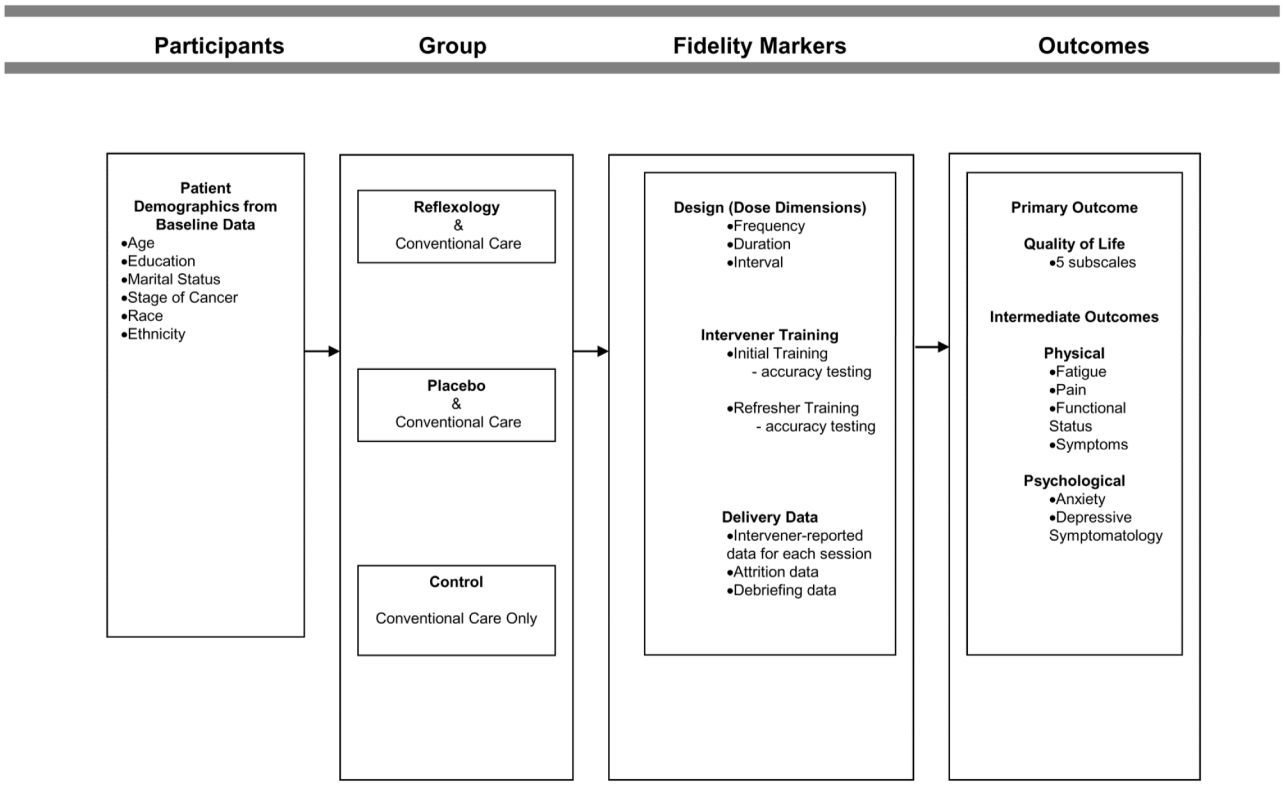

Figure 1.
Study Design for Intervention Fidelity

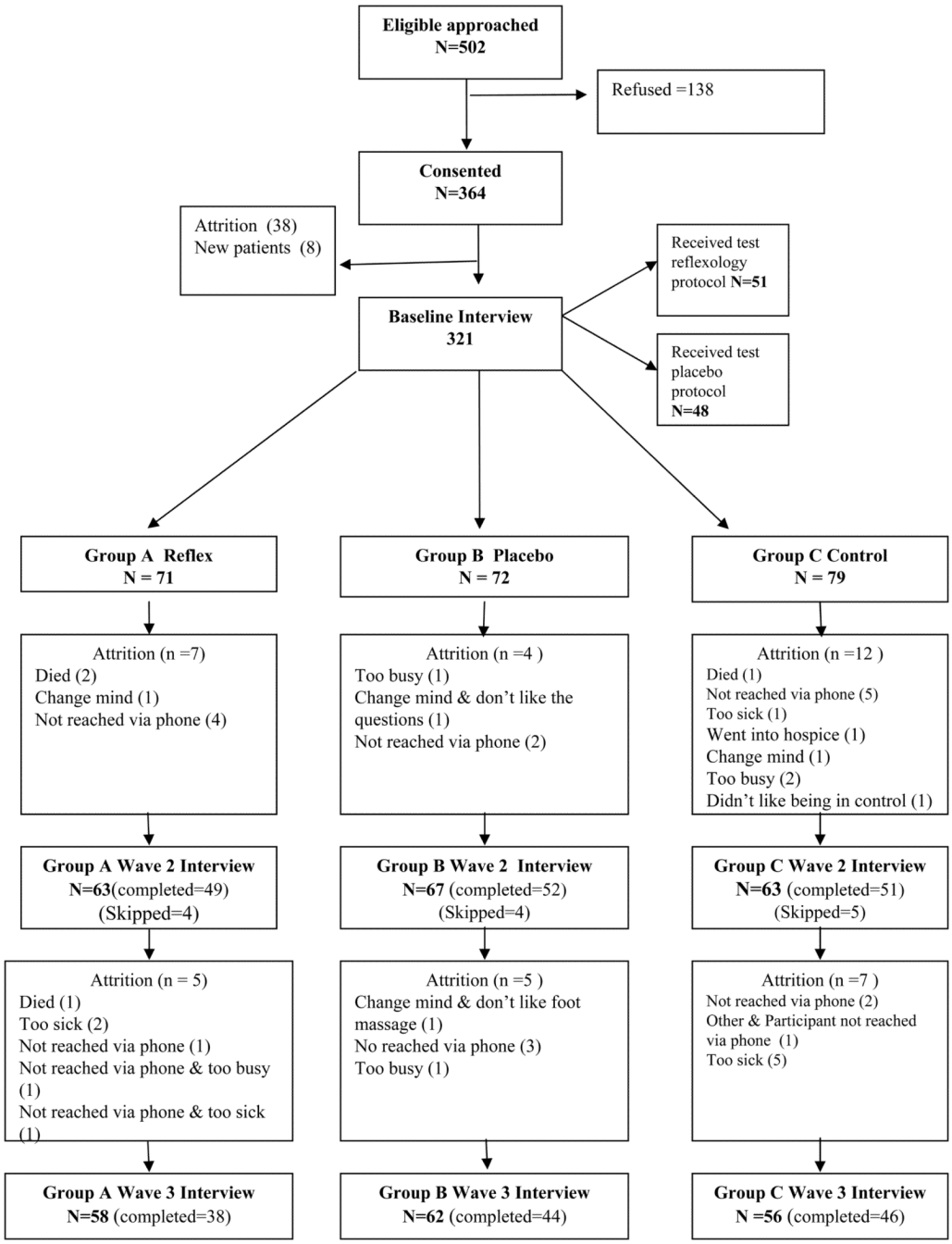

Figure 2.
Flowchart of the Study

Encounter **Date** ___/___/___
1 2 3 4
(circle one)

Day of Week: ___Su ___Mo ___Tu ___We ___Th ___ Fr___ Sa
Time of Day: ___am ___pm
Location: ___clinic ___home ___other, specify_____

Reason unable to do session:
___none
___patient too tired
___patient not at appointed location
___IV in foot or ankle area
___feet or ankles bruised
___patient died
___patient hospitalized
___patient cannot be reached
___other, describe_____

Social Interaction During session:
Was there any difficulty maintaining the protocol for social interaction?

___YES ___NO
↓
___patient was very talkative

___patient asked multiple questions

___other, describe_____

Comments expressed by patients related to protocol:
___none
___too light
___too deep
___too long
___just right
___pleasant
___too short
___relaxing
___other, describe_____

General concerns reported to P.I.:_____
Date___/___/___ Time:_____

Safety concerns reported to P.I.:_____
Date___/___/___ Time:_____

Drop out
Date___/___/___ Reason:_____

Patient initiated calls between encounters
Date:____/____/____ Reason:_____

Figure 3.
Patient Encounter Form

Table 1

Patient Demographics

Category	Reflexology Group (N=71)	Placebo Group (N=72)	Control Group (N=79)
	Mean (StDev)	Mean (StDev)	Mean (StDev)
Age	55.68 (9.22)	55.72 (11.34)	58.51 (12.23)
	N (%)	N (%)	N (%)
Education			
High School or Less	12(16.90)	19(26.39)	26(32.91)
Some College	18(25.35)	22(30.55)	22(27.85)
Completed College or Graduate/Professional Degree	39(54.93)	30(41.67)	30(37.97)
Missing	2 (2.82)	1 (1.39)	1 (1.27)
Marital Status			
Refused/Never Married	9(12.68)	12(16.67)	8(10.13)
Married or Living with Partner	51(71.83)	47(65.28)	53(67.09)
Divorced/Separated	5(7.04)	9(12.5)	10(12.66)
Widowed	5(7.04)	4(5.56)	8(10.13)
Race			
Caucasian/White	61(85.92)	59(81.94)	71(89.87)
Black	10(14.08)	11(15.28)	7(8.86)
Other/missing	0(0)	2(2.78)	1(1.27)
Ethnicity			
Hispanic or Latino	0(0)	2(2.78)	1(1.27)
Not Hispanic or Latino	71(100)	70(97.22)	77(97.47)
Recurrence			
No	29(72.5)	28(63.64)	43(76.79)
Yes	11(15.4)	16(36.36)	13(23.21)
Missing	31 (27.5)	28 (11.1)	23 (29.11)
Metastasis			
No	17(23.94)	19(26.39)	17(21.52)
Yes	54(76.06)	53(73.61)	62(78.48)
Stage of Cancer			
III	20(28.17)	26(36.11)	21(26.58)
IV	28(39.44)	29(40.28)	33(41.77)
Original Pathology Stage I or II with later recurrence or metastasis	19(26.76)	16(22.22)	21(26.58)
Missing	4(5.63)	1(1.39)	4(5.06)

Table 2

Reflexology & Placebo Groups Intervention and Debriefing

	Reflexology	Placebo
	N (%)	N (%)
Number of sessions completed*		
4	54 (84.38)	54 (88.52)
3	3 (4.69)	4 (6.56)
2	1 (1.56)	2 (3.28)
1	5 (7.81)	1 (1.64)
0	1 (1.56)	0 (0.00)
Correct guess of group assignment**	32 (82.05)	19 (46.34)

*Patients in progress: 7 in reflexology group, 11 in placebo group.

**Out of patients who completed the last interview: 39 in reflexology group, 41 in placebo group. P-value for the test of group differences is .0002.