

Methodological Issues in Trials of Complementary and Alternative Medicine

Interventions

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1 **Abstract**

2 **Background:** Complementary and alternative medicine (CAM) use is widespread among cancer
3 patients. Information on safety and efficacy of CAM therapies is needed for both patients and
4 health care providers. Well-designed randomized clinical trials (RCTs) of CAM therapy
5 interventions can inform both clinical research and practice.

6 **Objectives:** To review important issues while designing RCTs in CAM interventions.

7 **Method:** Using a National Cancer Institute-funded reflexology study as an exemplar, this paper
8 reviews issues dealing with the identification and selection of a target population, outcomes and
9 measures, dose parameters, number of trial arms, and randomization.

10 **Results:** Trials of CAM interventions designed and implemented according to appropriate
11 methodological standards will facilitate the needed scientific rigor in CAM research.

12 **Discussion:** CAM interventions can be tested using proposed methodology, and the results of
13 testing will inform nursing practice in providing safe and effective supportive care and
14 improving the well-being of patients.

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Introduction

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2 Patients have been using complementary therapies since before the beginning of nursing
3 as a profession (American Nurses Association & American Holistic Nurses Association, 2007);
4 however, it has only been since the early 1990s that health care providers have acknowledged
5 their widespread use (Eisenberg et al., 1993). Initially regarded as health care interventions that
6 were neither routinely taught in medical schools nor available in treatment facilities, the use of
7 complementary and alternative medicine (CAM) has become prevalent (Barnes, Powell-Griner,
8 McFann, & Nahin, 2004), with estimates of roughly 1 in 3 people in the United States (or 72
9 million adults) using CAM within the past year (Tindle, Davis, Phillips, & Eisenberg, 2005).
10 Despite its popular use as an adjunct to traditional medical services, the vast majority of CAM
11 users do not disclose this to their health care providers (Eisenberg et al., 2001), and rates of
12 patient non-disclosure among members of ethnic minority groups are even lower (Chao, Wade,
13 & Kronenberg, 2008). This communication breakdown can lead to potentially negative treatment
14 ramifications due to interaction effects between conventional and unconventional approaches
15 (Hu et al., 2005). Finally, out-of-pocket expenditures for CAM are estimated at roughly \$34
16 billion dollars annually (MacLennan, Wilson, & Taylor, 2002). Although only a decade ago this
17 figure was comparable to out-of-pocket expenditures for conventional U.S. medical care
18 (Eisenberg et al., 1998), CAM therapies appear to be increasingly affordable in comparison due
19 to skyrocketing health care costs, insurance premiums, and out-of-pocket payments (Pagan &
20 Pauly, 2005). With such high rates of use, it is vital that reliable information is available
21 regarding the safety and efficacy of CAM therapies. Although many CAM therapies offer safe
22 and effective care, others may pose risks that health care providers must discuss with patients

1 (Angell & Kassirer, 1998; Tagliaferri, Cohen, & Tripathy, 2001). Well-conducted CAM research
2 is needed to inform evidence-based clinical practice.

3 To date, many CAM therapy research findings have been inconsistent due to a lack of
4 standardization in the design and scientific methodology of trials. Early studies were at the
5 descriptive level and included heterogeneous populations of patients (Willison & Andrews,
6 2004). While there is debate on how best to study CAM (Berman & Straus, 2004; Buchanan et
7 al., 2005; Efficace et al., 2006), randomized clinical trials (RCTs) can provide valid and reliable
8 evidence that informs clinical research and practice (Ospina et al., 2007). In particular, CAM
9 therapies can be offered as supportive care in treatment of cancer and other chronic conditions
10 (Ernst, Schmidt, & Baum, 2006; Gerber, Scholz, Reimer, Briese, & Janni, 2006).

11 In a comprehensive review conducted in 2005, the number of RCTs of CAM
12 interventions was almost 4 times smaller than the number of trials of conventional medicine
13 interventions (Klassen, Pham, Lawson, & Moher, 2005). The same ratio of approximately 4:1
14 holds for published systematic reviews of conventional medicine versus CAM interventions
15 (Lawson, Pham, Klassen, & Moher, 2005). Studies in CAM that utilize RCT design rely upon
16 methods that are identical to other RCTs and can adhere to the same standards as RCTs of
17 conventional medicine interventions. However, some of the specific methodological issues are
18 unique and particularly difficult to address with CAM therapies. A comprehensive review by
19 Efficace and colleagues (2006) concluded that methodological quality of patient-reported
20 outcome research in CAM RCTs in oncology is low.

21 The purpose of this paper is to highlight important methodological issues while
22 conducting RCTs with CAM therapies, with a special focus on: 1) reviewing the challenges in
23 designing RCTs with CAM therapies; 2) providing examples of approaches that can address

1 these challenges; and 3) identifying areas where further research is needed to improve the rigor
2 of RCTs conducted with CAM therapies. To illustrate the basic principles of sound CAM
3 research methodology within an RCT, a National Cancer Institute-funded multi-site study
4 currently being conducted by the authors (*Reflexology: An Intervention for Advanced Breast
5 Cancer, R01, CA104883*) will be used as an exemplar. This study targets women with advanced
6 breast cancer undergoing chemotherapy, who upon consent and completion of a baseline
7 interview, are randomized into one of three arms: reflexology, placebo, or control. Reflexology,
8 the CAM intervention evaluated in this RCT, is defined as a method of using the thumb on reflex
9 areas of the feet which correspond to the glands, organs, and parts of the body (Byers, 1996).
10 Women in reflexology and placebo groups are blinded to their group assignment and receive four
11 standardized weekly foot sessions delivered by specially trained interveners (reflexologists or
12 placebo providers). Data on primary outcomes of quality of life (QOL) are collected at three time
13 points: baseline; immediately following a series of foot sessions (7 weeks after baseline); and 13
14 weeks after baseline. To date, the study has enrolled 230 women with the target recruitment of
15 390.

16 **Method**

17 The characteristics of interventions undergoing testing lead to specific issues and
18 challenges investigators must address when designing RCTs of CAM therapies. These issues
19 include the choice of: 1) whether the target population is appropriate for a specific therapy; 2)
20 outcomes that can potentially be impacted by a CAM therapy being tested as well as the
21 instrument selection; 3) the dose of the intervention, with dimensions including the number of
22 sessions of the intervention, the duration of each session, and the amount of time between
23 sessions; 4) the timing of longitudinal assessments; 5) the number of trial arms; and 6)

1 randomization. The focus of this paper is on the discussion of these issues using the reflexology
2 RCT as an exemplar.

3 **Choice of a Target Population**

4 As with any intervention, the choice of a target population is important. While the use of
5 CAM therapies has been growing in recent decades (Kessler et al., 2001), there are certain
6 subgroups of the population that are much more or much less likely to be interested in
7 participating in CAM studies. Examples of subgroups of people who are more likely to be
8 interested include women (Richardson, Sanders, Palmer, Greisinger, & Singletary, 2000), people
9 with at least some college education (Cassileth, 1999; Boon, Olatunde, & Zick, 2007), people
10 with specific health problems (Astin, 1998; Molassiotis et al., 2006), and youth (Cassileth &
11 Vickers, 2005). Further, there may be subgroups of patients who may be initially interested and
12 consent to participate in a trial but drop out before completing the study. Among women with
13 advanced breast cancer, one such subgroup in the reflexology trial is black women (Sikorskii,
14 Wyatt, & Siddiqi, 2008, under review). Pilot data are critical in providing such information that
15 can be used in designing a RCT.

16 The importance of pilot data is best demonstrated by a quasi-experimental study that
17 informed the current reflexology RCT. When cancer patients were offered a choice of one or
18 more CAM therapies, those with lower well-being and higher levels of anxiety were attracted to
19 guided imagery (Wyatt, Sikorskii, Siddiqi, & Given, 2007a). The attrition rate among those who
20 chose this therapy was 41%, and those who dropped out reported significantly worse symptoms
21 of depression, anxiety, and physical well-being compared to those who stayed in the guided
22 imagery group. Such results would threaten the external validity of the findings in a RCT
23 because of attrition bias, or reliance on the assumptions of missing data techniques, which are

1 not always verifiable (Senn, 2007). In addition, without a high attrition rate, an RCT would have
2 high cost from wasted research resources spent on participants who did not provide follow-up
3 data.

4 One approach to ensuring external validity of the RCT finding is specifying the set of
5 inclusion and exclusion criteria reflecting the target population likely to benefit from the
6 intervention. For example, a pilot study conducted with a heterogeneous population of cancer
7 patients (Wyatt, Sikorskii, Siddiqi, & Given, 2007b) found that more women than men were
8 interested in reflexology, and women with breast cancer were more interested than women with
9 other solid tumors.

10 **Outcome & Measures**

11 Patients turn to CAM therapies for a variety of reasons, one of which is seeking to
12 improve QOL and manage symptoms from diseases or treatments. It was recently reported that
13 more than 80% of women diagnosed with breast cancer turn to CAM for symptom management
14 (Boon et al., 2007). The choice of QOL as a primary outcome in a CAM therapy trial is
15 consistent with patients' goals to reduce disease or treatment-related symptoms and side effects
16 and improve health-related QOL. In addition, using QOL as a primary outcome of a CAM
17 therapy trial is supported by regulatory agencies such as the Food and Drug Administration
18 (U.S. Department of Health and Human Services (FDA), 2006) and, specifically in cancer, by the
19 American Society of Clinical Oncology (American Society of Clinical Oncology, 2001).

20 Ferrell, Wisdom, and Wenzl (1989) were early to recognize QOL as a multidimensional
21 construct, but at the time found no consensus in the literature on the specific dimensions of QOL.
22 Over the past two decades, the QOL literature has shifted to the term health-related QOL, which
23 refers to the level of well-being and satisfaction associated with an individual's life and how

1 these are affected by disease, accidents, and treatments (Cella & Tulsky, 1993; Wyatt &
2 Friedman, 1996). In the exemplar reflexology study, health-related QOL is conceptualized as a
3 holistic multidimensional interaction of life domains: physical, psychological, social, and
4 spiritual (Wyatt et al., 1996). Within each QOL domain, it is important to recognize specific
5 components. In conceptualization proposed by Wilson and Cleary (1995), the components of
6 QOL are symptoms, functional status, and general health perceptions, such as satisfaction with
7 life. Each of the QOL domains (physical, psychological, spiritual, social) contains these
8 components associated with one another. For example, higher levels of symptom severity have
9 been shown to be associated with worse functioning (Dodd, Miaskowski, & Paul, 2001; Fu,
10 LeMone, & McDaniel, 2004; Ganz et al., 2004; Lee, Dibble, Pickett, & Luce, 2005; Sarna et al.,
11 2004). Among cancer patients in particular, reduction in symptom severity can help maintain
12 treatment regimen and may ultimately affect survival (Campagnaro et al., 2008; Kurtz, Given,
13 Kurtz, & Given, 1994). The most prevalent symptoms reported by breast cancer patients in the
14 exemplar reflexology study include fatigue, weakness, pain, insomnia, peripheral neuropathy,
15 poor appetite, change in taste, dry mouth, difficulty concentrating, memory problems,
16 restlessness, and mood changes. Associations exist among multiple symptoms, and a holistic
17 approach of treating the mind, body and spirit is at the center of CAM. Assessments of multiple
18 symptoms and other QOL components of the QOL domains can be included as part of the trial
19 design. Pointed out in a review article by Cleeland (2007), a measure of symptom burden created
20 by multiple symptoms may be a sufficient outcome particularly in populations experiencing
21 deterioration in health; for example, end of life populations where an improvement in QOL may
22 not be expected. Although a link between symptoms and other QOL components (functioning
23 and general health perceptions) exists (Miaskowski et al., 2007), a reduction in symptom burden

1 by a CAM therapy intervention may be achieved with or without an immediate impact on other
2 QOL components, just as is the case with trials of pharmacological interventions(Sloan et al.,
3 2007). If a CAM therapy is proven to reduce severity of a specific symptom or symptoms, it is
4 beneficial to patients even if other QOL components fail to improve (Jatoi, Kumar, Sloan, &
5 Nguyen, 2003). In the reflexology study, measures of pain and fatigue (Cleeland & Ryan, 1994;
6 Mendoza et al., 1999) are included, as well as measures of other multiple symptoms commonly
7 reported by women with breast cancer undergoing chemotherapy. Many of the published CAM
8 studies focus on symptoms, but the drawback is concentration on a single symptom or a few
9 symptoms without considering a patient's total symptom burden.

10 Since symptom and QOL ratings come from the patient perspective, the use of patient
11 reported outcomes (PROs) is a logical approach to assessment and monitoring (Lipscomb, Gotay,
12 & Snyder, 2007; Trotti, Colevas, Setser, & Basch, 2007). Kirkova et al. (2006) summarize the
13 large number of available QOL instruments in a comprehensive review. Challenges faced by
14 investigators related to the inclusion of symptoms and QOL, as well as other PROs in RCTs
15 described in the literature, and apply to both CAM trials and conventional medical interventions
16 (Efficace et al., 2003; Sloan et al., 2007). One challenge is stating an a priori hypothesis about
17 expected changes in PRO endpoints due to the intervention (Efficace et al., 2006). CAM
18 therapies have the potential to affect multiple symptoms have not been identified (Cleeland,
19 2007). One way to address changes in symptoms is through responder analysis, a method that
20 uses anchor-based definitions of patient responses to multiple symptoms that may be interrelated
21 as a function of disease, its treatment, or comorbid conditions (Miaskowski et al., 2007;
22 Sikorskii, Given, You, Jeon, & Given, 2008). This approach interfaces categories of symptom
23 severity (mild, moderate, severe) with levels of symptom interference on enjoyment of life,

1 relationships with others, general daily activities, and emotions. Responder analysis can enable
2 the aggregation of multiple symptoms within patient via generalized estimating equations
3 technique (Zeger, Liang, & Albert, 1988). For example, when effect of a CAM symptom
4 management intervention is evaluated, some symptoms may be more responsive than others and,
5 depending on their association with other symptoms, may indirectly lower severity of other
6 symptoms. Moreover, some patients may respond differently to interventions directed at
7 different combinations of symptoms at varying severity levels, thus requiring more or less time
8 to resolve different sets of symptoms.

9 Ideally, outcome data should be collected longitudinally at time points that not only
10 include baseline and post-intervention times, but also the time points when intervention was
11 delivered. Following each intervention session, PRO data and provider-reported data on delivery
12 of the intervention can be collected (Basch et al., 2006). Analysis of these data can provide
13 results on intervention deconstruction documenting when and how changes in outcomes occur,
14 so that the intervention does not represent a “black box” with changes documented only after the
15 end of the intervention. The results of longitudinal analyses of intervention sessions can begin to
16 shed light on mechanisms of action of CAM therapies by answering questions about when and
17 how changes in QOL occurred and which symptoms and group of symptoms responded to
18 interventions under examination. With an exploratory study, data from each intervention session
19 can inform planning of a large-scale trial in terms of the number of encounters needed to achieve
20 a clinically meaningful effect.

21 Recent literature suggests there may be common biological mechanisms underlying
22 multiple symptoms (Cleeland, 2007; Lee et al., 2004). Pro-inflammatory cytokines have been
23 linked to some symptoms in animal models and some studies with humans (Myers, 2008). A

1 biological mechanism is one of the proposed explanations for clusters of symptoms in oncology
2 (Miaskowski, Aouizerat, Dodd, & Cooper, 2007). Inclusion of a biological measure in addition
3 to PRO assessment may strengthen the study design and allow for different mechanisms of
4 action to be identified through specific therapy affects, certain symptoms, symptom clusters, or
5 other QOL components.

6 In addition to understanding the influences of biological mechanisms on symptoms and
7 QOL components, assessing the use of health care services may be an important secondary
8 outcome. For example, with cancer patients, effective symptom management can be evaluated,
9 not only by assessing the effectiveness of a CAM therapy on symptom reduction or control, but
10 also through observing lower numbers of emergency room visits and hospitalizations due to
11 complications or symptom exacerbations. Another important effect of a CAM intervention may
12 be helping patients stay on treatment longer, without dose delays and reductions of
13 chemotherapy. These types of clinical data can be invaluable in placing greater “real world”
14 meaning and context behind a person’s self-reported fatigue or pain scores.

15 **Dose of the Intervention**

16 It is very difficult to quantify the intensity of many CAM therapies, especially energy or
17 mind-body therapies such as meditation or guided imagery. The definition of dose is clear for
18 CAM interventions from a biologically based category (see NCCAM Web site:
19 <http://nccam.nih.gov>) such as vitamins and herbal supplements. However, a rigorous definition
20 dose is also needed for RCTs of CAM therapies from other major CAM categories: mind-body
21 interventions, energy therapies, manipulative and body-based methods, and alternative medical
22 systems. In determining the dose, three critical dimensions have to be considered: number of
23 sessions of the intervention, the duration of each session, and the amount of time between

1 sessions. However, for most of the therapies mentioned, dose can be specified in terms of the
2 number of sessions delivered by the provider (e.g., for acupuncture) or self-administered by a
3 patient (e.g., for mindfulness meditation). For RCTs of CAM therapies, investigators must draw
4 from both the literature and clinical practice to determine the critical dosage dimensions. For
5 example, across the therapeutic touch (TT) literature, session duration has ranged in time from 3
6 minutes to 20 minutes (Hyams, Burke, Davis, Rzepski, & Andrulonis, 1996; van den Berg,
7 Benninga, & Di Lorenzo, 2006; Wyatt, Beckrow, Beckrow, & Pthal, 2006; Wyatt, Donze, &
8 Beckrow, 2004; Wyatt & Friedman, 1998). In many TT studies, only one session (n=10 studies)
9 was used; others used multiple sessions ranging from two (n=4 studies) to 10 (n=1 study)
10 sessions (Kissane et al., 2004; Lee et al., 1992; Wyatt et al., 2004; Wyatt et al., 2007b). The
11 majority of studies used between two and six. The frequency of session, which has ranged from
12 daily to weekly, covered from one day to six weeks (Kissane et al., 2004; Lee et al., 1992; van
13 den Berg et al., 2006; Wyatt et al., 2007b). Of the 21 experimental TT studies reviewed since
14 1981, only 2 studies used a time period of 6 weeks, and others used shorter time periods.

15 During planning of the exemplar reflexology study, review of the reports of the three other
16 reflexology studies conducted in the U.S. (Ernst & White, 2000; Oleson & Flocco, 1993;
17 Stephenson, Weinrich, & Tavakoli, 2000) revealed that duration of session dose has varied from
18 30 to 40 minutes, with the two cancer-specific studies using the 30-minute sessions. In addition,
19 these three studies conducted one to eight treatments per study, so this wide variation provided
20 less guidance on frequency of sessions. The two cancer studies, however, used either one or three
21 treatments. In our pilot work with 100 cancer patients (Wyatt et al., 2007a) the weekly sessions
22 and were evaluated, and significant changes on key outcome variables such as QOL were
23 observed. Therefore, based on the pilot work, the existing literature, and the expert's dose

1 recommendation (drawn from expert's 22 years of reflexology practice as a certified
2 reflexologist), we implemented the dose of one time per week for 4 weeks (30 minutes per
3 treatment). In determining the dose, the choice made about the primary outcome has to be
4 considered because the number of sessions and duration of the intervention have to be adequate
5 to allow the meaningful change to occur in primary and secondary outcomes.

6 **Timing of Longitudinal Assessments**

7 Dose considerations are naturally tied to the issue of timing of the assessments. First, as
8 mentioned before, it is extremely informative to obtain PROs following each session of the
9 intervention delivery. These data can answer questions regarding when the changes in the
10 outcomes begin to happen and when these changes reach statistical and clinical significance.
11 Using responder analysis, response and time to response can be assessed. Notably, while time to
12 event type of outcomes such as survival time, time of disease-free survival, time to recurrence or
13 time to treatment failure have been used in studies testing effects of various conventional
14 medicine interventions (Allegra et al., 2007; Punt et al., 2007). RCTs of CAM interventions have
15 not included time to response or time to other events as outcomes.

16 Second, once the effect is achieved, the next question is whether it is sustained over a
17 period of time that is important from patients' and clinicians' perspectives. If a cancer patient is
18 undergoing chemotherapy and turns to CAM for symptom management, will the supportive
19 effect achieved by CAM last through the end of the chemotherapy cycle or course? Is symptom
20 relief sustained over a period of time so that it can be reflected in better global QOL rating?
21 These and other questions have to be taken into account when determining timing of follow-up
22 assessments.

23 **Distinguishing therapeutic and placebo effects**

1 As with conventional medicine interventions, efforts must be made in CAM RCTs to
2 examine the slippery slope of the added attention versus therapeutic effects. However, the
3 techniques for achieving this may be therapy-specific and differ from techniques used with
4 conventional medicine interventions. For example, a placebo pill frequently used in drug trials
5 may not be easily chosen in trials of herbal supplements with distinct smells that most people are
6 familiar with, for example, ginger (Hickok, Roscoe, Morrow, & Ryan, 2007; Zick et al., 2008).

7 The placebo session should include all the same phases as the experimental CAM session,
8 i.e., preparation for session, timing of the session, and concluding the session. The placebo,
9 however, should not involve any of the “active ingredients” of the experimental CAM
10 intervention but should appear similar if not equal. The placebo technique used by Quinn (1988)
11 is a good example to follow, whereby the placebo arm mimicked the movements of a TT
12 practitioner, but unlike TT, the nurse does not enter a meditative state, has no intention to assist
13 the patient therapeutically, has not attuned to the condition of the patient, and engages in no
14 direction of energy to the patient. In the exemplar reflexology trial, placebo group participants
15 receive a foot manipulation that does not target specific reflexology points of the foot, and does
16 not utilize techniques specific to reflexology. However, while avoiding active elements of
17 reflexology, placebo participants may experience a therapeutic effect above and beyond attention
18 through human touch and massage-like manipulation. The positive effects of massage have been
19 documented using PROs and biological markers (Institute of Medicine, 2005). The inclusion of a
20 control group in the design provides statistical control over the changes in QOL and mediators of
21 QOL over time that occur from natural course of disease and its treatment and will allow us to
22 attribute the improvement in QOL to the intervention rather than to other factors.

23

1 **Minimizing Extraneous Influences**

2 In many types of mind-body CAM interventions (e.g., massage, TT, reflexology), the
3 influence of social supportive factors can also potentially contribute (and add noise) to the
4 therapeutic effect of the treatment. In designing CAM RCTs, it is important to provide
5 standardized training to treatment and placebo providers to not only instruct on the manualized
6 scope of the intervention, but also to address the leveraging and management of interpersonal
7 interactions that may occur during the treatment itself. Treatment and placebo interveners should
8 be instructed not to initiate any conversation once the intervention begin but rather to instruct the
9 patient to relax and close his or her eyes. If questions are asked about the disease condition, the
10 session, or disease therapy, patients should be referred back to their primary physician. If the
11 patient persists in conversation, the topics should be kept general, such as weather or current
12 events, responding with closed-ended comments. Training should also include didactic
13 information, written steps, role-playing, demonstrations, and return demonstrations based upon
14 an established protocol criterion for the treatment. Should multiple sites be involved, there
15 should be quality assurance visits at all sites on a regular basis to determine that all intervention
16 protocols are being administered uniformly.

17 **Discussion**

18 This article summarizes important methodological issues while designing and
19 implementing clinical trials of CAM interventions. Given the increasing use of CAM to support
20 conventional medicine, it is critical that exploratory, dose-ranging, and efficacy trials adhere to
21 certain common practices to ensure the highest degree of standardization possible. This includes
22 the purposeful selection of the target population, endpoints and outcome measures, dose
23 intensity, timing of assessments, study design safeguards, and analytic approaches.

1 Following these methodological guidelines will contribute to the growing evidence base
2 of potential CAM interventions available to nurses in clinical practice. The exemplar reflexology
3 study described throughout illustrates how these methods can be effectively implemented to
4 bring transparency to formerly mysterious practices.

5 Designing and conducting CAM interventions can be challenging and requires a great
6 deal of forethought and planning to account for the myriad threats to internal and external
7 validity often inherent to many of these practices. Although a certain degree of study design
8 flexibility can be necessary to maintain the integrity of a CAM intervention in a clinical trial, the
9 methodological approaches we have highlighted can be incorporated with little to no effect on
10 the overall authenticity of the CAM practice under review.

11 As nursing professionals continue to maintain the frontline of today's ever-changing
12 health care environment, being equipped with an armament of effective CAM tools can help to
13 reinforce and support the lives of patients and their caregivers.

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