

Reviewer Comments:

Reviewer #1: STRENGTHS

As the authors point out, CAM therapies are often used by people with cancer, yet there is a significant need to determine the efficacy and safety of many of these therapies. The importance of producing evidence to support their use, if appropriate, cannot be overemphasized, if CAM therapies are to achieve acceptance in the general health care environment. The gold standard for the highest level of evidence is the RCT, thus well-conducted RCTs of CAM therapies are desperately needed. A paper describing some of the issues and challenges to be considered in designing CAM RCTs, along with potential solutions, is a welcome addition to the literature.

Some of the issues that are described in this paper (e.g., choice of target population, outcomes and measures, intervention doses) are particularly germane for researchers in this field. The use of an ongoing federally funded RCT of a CAM as the exemplar is an excellent way to demonstrate how some of these key issues can be dealt with in an actual study. The paper has the potential to make an important contribution to the methodological literature, however, several important areas need to be addressed in a revision.

AREAS FOR IMPROVEMENT/REVISION

The major concern in this paper is the lack of an obvious overarching conceptual framework to guide the discussion. Throughout the paper the authors mention things like "appropriate methodological standards" (in the abstract), the "same standards of RCTs of conventional medicine interventions" (in the introduction), "basic principles of sound CAM research methodology within an RCT" (introduction), "external validity" (in "Choice of a Target Population"), etc. However, nowhere do they provide a single overarching framework related to the design and conduct of methodologically rigorous RCTs, using CAM or other interventions. While most of the challenges that are discussed are, as noted above, highly germane, the use of an accepted framework for scientific rigor would significantly enhance the authors' ability to focus this paper and explicate the potential issues within such a framework.

In the section entitled "Method", the authors list six areas for discussion, but do not indicate why they selected these particular areas, nor do they describe any particular "methods" for the paper. Was a literature review performed on methodological issues in CAM intervention studies, or is the paper mostly anecdotal? As currently written, the paper seems to be a relatively arbitrary selection of topics, and in fact, leaves out other highly significant challenges. For instance, treatment fidelity is not dealt with in any obvious way, yet it is essential in any RCT, but particularly in CAM RCTs given the need for evidence. Another critically important area that is not discussed is that of controlling for, or recognizing and measuring, potential confounding variables that might interfere with the investigator's ability to attribute improvement in outcomes to the CAM therapy

being tested. For example, if CAM therapy is used to treat a symptom, how does the investigator control for (or otherwise deal with) pharmacologic interventions for the same symptom? And what about other clinical variables that may influence symptom outcomes--how do CAM researchers deal with these?

Several sections of the paper seem to fall short in providing substantive discussion. For example, "Choice of a Target Population" concludes with a very short paragraph regarding inclusion/exclusion criteria to improve external validity. The second and last sentence of the paragraph mentions a pilot study, however, there is no further discussion that would help investigators consider the various strategies and other issues they must consider in selecting their inclusion/exclusion criteria. The use of this pilot study as an apparent exemplar would be enhanced if the implications were detailed here.

The section entitled "Outcomes and Measures" is good, but would be considerably more helpful if the concept of "symptom burden" was better explicated, and the focus of the discussion clarified and tightened. The discussion of symptoms, CAM interventions, and intervention deconstruction is somewhat confusing and diffuse. The last two paragraphs of this section seem underdeveloped and under-referenced.

The section entitled "Timing of Longitudinal Assessments" seems somewhat redundant with earlier text, and the first paragraph is unclear with respect to "...time to event type of outcomes..."; what is it that the authors are trying to say here?

The section entitled "Distinguishing Therapeutic and Placebo Effects" is interesting and important, however, the question of an attention control group comes to mind here—is this a concept worth discussing in this section, instead of just the concept of the placebo group? The reference to the exemplar study (second paragraph, last sentence) is confusing. Again, more explication of implications for other CAM researchers would be most helpful here.

Finally, the section titled "Discussion" appears to be more of a summary than a discussion. The first paragraph lists several topics that were discussed, including "study design safeguards" and "analytic approaches" yet these were not clearly identified nor thoroughly discussed. The words "...certain common practices..." (in efficacy trials) and "...highest degree of standardization possible..." in this paragraph again raise the question of: What framework are the authors using to organize their paper, if any?

In revising this paper, this reviewer strongly recommends that the authors review and consider several possible frameworks for enhancing scientific rigor in the design, conduct, and analysis of experimental and quasi-experimental research. They should select an appropriate framework and then use it to guide the organization, structure, content, and focus of this paper. Putting their important thoughts and excellent hands-on experience into a published, accepted methodological framework will significantly enhance the focus, content, and ultimate contribution of this paper to the literature, and to other CAM researchers. Such potential frameworks could include, but are not limited to:

- 1) the CONSORT (Consolidated Standards of Reporting Trials) framework (see

CONSORT website found via Google); 2) study validity (Experimental and Quasi-Experimental Designs for Generalized Causal Inference, by Shadish, Cook, & Campbell, 2002); or 3) assessment criteria for rating the quality of evidence for clinical practice guidelines (e.g., Hadorn et al., 1996, *Journal of Clinical Epidemiology*, 49, 749-754).

Reviewer #2: General Review

1. The topic of this manuscript, methodological issues that need addressed in randomized clinical trials, has particular significance to beginning and seasoned nurse scientists. This manuscript addresses these issues from both a practical and scientific perspective. It is important that these issues are addressed to inform both clinical research and practice. This manuscript will also be appreciated by oncology nurses who use complementary therapies in their plan of care. The topic is very timely and *Nursing Research* is an appropriate journal to disseminate these findings.
2. The title, *Methodological Issues in Trials of Complementary and Alternative Medicine Interventions*, is representative of the manuscript. The abstract is well written and informative.
3. The majority of references cited are within the past eight years. A few references are older, but seem appropriate. References are cited correctly in-text in APA format. The reference list is extensive and provides the reader with excellent resources.
4. The content is research based. The manuscript is well organized, well-written, and easy to comprehend.
5. No tables or figures were included. Although tables could be created to complement the manuscript, I do not think it's necessary for this type of manuscript.

Research Report --- Specific Comments

1. Introduction/background - This manuscript addresses many important methodological issues that must be considered when designing and implementing a clinical trial of complementary and alternative medicine interventions (CAM). The introduction sets the stage by providing the reader with background information in regard to the incredible number of people who utilize CAM interventions, advantages, and also the breakdown in communication between those who use CAM and health care professionals. The purpose of the manuscript is clearly stated. Reflexology is used as the exemplar CAM intervention and Quality of Life is described as the dependent variable or outcome measure.
2. Method - A clear description of the specific issues and challenges that will be addressed in this section is clearly delineated and included: 1) target population; 2) outcomes and measures; 3) timing of longitudinal assessments; 4) distinguishing therapeutic and placebo effects; and, 5) minimizing extraneous influences. Each of these sections is very well organized and written, providing the reader with an explanation as to why each issue/challenge needs addressed when planning a randomized clinical trial. Ways by which to address each issue is discussed and examples are included.

The authors chose to use a federally funded study to address the methodological issues

and challenges in developing a randomized clinical trial. This was a really creative way by which to discuss these issues and help other researchers see the benefits of a well-designed clinical trial. This will also be important for the staff nurse and others to better understand how to critique and critically examine other clinical trial reports that may influence evidence-based nursing practice.

The use of quality of life tools and interpretation issues is thoroughly discussed. This section is comparatively longer than the other sections, but provides the reader with a wealth of information about quality of life measures. The importance of designing a placebo similar to the intervention and including a placebo group in addition to the control and intervention group is also well received, as is ways by which researchers determine the most appropriate timing and dosage of the intervention.

3. Discussion

The authors conclude with the Discussion section. They summarize in a very succinct way the importance of designing and implementing clinical trials, specifically for CAM.

This manuscript was a pleasure to review. Its practical application to developing a clinical trial was very informative and clarified some issues I have questioned overtime.

CHECKLIST FOR STYLE

TITLE PAGE --

Supply running head of less than 50 characters (no abbreviations).

REFERENCES -- Reduce number of references to 40 - presently there are 78.

Update REFERENCE LIST using APA 5th Ed. format. In particular, use hanging indent.