Author's response to reviews

Title: Patient education integrated with acupuncture for relief of cancer-related fatigue: Randomized controlled feasibility study

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Author's response to reviews: see over
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Melissa Norton, MD
Editor in Chief
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We find the reviewer comments to be very useful. We thank the reviewers for generously investing their time in helping us to improve this manuscript on patient education combined with acupuncture to relieve cancer-related fatigue. In the attached document, we summarize reviewer comments and provide a point-by-point response to their concerns.

Warm regards,
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**Summary of reviews and responses**

**Suzanna Zick Reviewer Report**

**Overall**

A. **Focus on recruitment strategies is “uninformative and unoriginal”**
   
   We have provided a more balanced presentation that describes the intervention, reports on recruitment, and provides results.

B. “**suggest the authors focus on the effect of BFI via the multi-modal aspects of their study”**
   
   We discuss the multi-modal aspects of the intervention in greater detail (see Intervention, pages 9-12, and Tables 1 and 2, pages 30-34).

C. **“Please, check tenses and change appropriately throughout the manuscript”**
   
   We changed the manuscript so it refers consistently to the past tense.

**Introduction**

A. **Description of the rationale for and the first objective is wordy**
   
   We have condensed the description of the first objective to note that the intent was to develop a theoretically-informed treatment protocol that integrated patient education with acupuncture (see p. 7).

B. **The last sentence of the introduction [which concerns the motivation for the objective on preliminary results] is confusing and does not follow from the previous sentence stating the second objective**
   
   We have re-written the last sentence to read: “A National Cancer Institute Community Clinical Oncology Program team concluded that small-scale studies are of critical importance for improving evidence-based assessments of CAM treatment regimens” (p. 8).

**Methods**

A. **Why were hypothyroidism, hepatitis, and other potential causes of fatigue not listed as exclusion criteria?**
   
   The inclusion/exclusion criteria were designed to be consistent with an earlier published study on acupuncture for cancer-related fatigue:
   
   
   We have noted in the discussion that not all potential causes of fatigue were excluded. (page 19)
B. Did participants need to be free of active cancer at time of enrollment into the study? Please state explicitly.
We now state that to be included in the study patients needed to be “finished with primary therapy for breast cancer (free of cancer)” (p. 8)

C. For the intervention, provide considerable more detail about the life style changes offered to participants in the areas of exercise, nutrition, etc.
   Take for example, exercise: Reviewer would like to know the exact details of the type of exercise, how frequently the exercise should be performed, how the exercise was explained to the participants, if the recommendations were individualized or standardized, and how were these interventions monitored
We have described the intervention in much greater details (see pages 9-12 and Tables 1 and 2).

D. Add in STRICTA
Added (Table 2).

Outcome
A. Authors should discuss how they determine if recruitment strategies were effective, what was measured and what was considered success.
We have re-written the recruitment methods to convey that we implemented a trial-and-error approach after it became clear that our chosen recruitment method would not accrue patients as expected, (page 9-10)

B. Were adverse events or compliance treated as outcomes? Were these assessed or recorded? If yes, please include in the manuscript.
We state in the final sentence of the results section that:
The clinician performing acupuncture (J JL) was provided a standardized checklist to assess for adverse events after each treatment, including bruising at needling site, panic, severe disorientation, fainting, infection, or puncture of an internal organ. The reports indicated that the acupuncture treatments caused no adverse events. (page 16)

Statistical methods
A. Please discuss how descriptive statistics were handled (baseline characteristics).
We used independent group t-tests. This is now noted in the text on page 15 and in a footnote to Table 3.

B. Discuss the statistics used to assess the recruitment strategy
We did not assess effectiveness of recruitment strategies.

C. Discuss how the statistics for the adverse events and compliance were handled.
As noted above, no adverse events were reported. Compliance was assessed by IK during the 2nd, 3rd, and 4th visits but her assessments were not systematically recorded. Instead, she used her assessments to help patients improve compliance. We state, in the limitations section, that compliance should be more formally assessed

D. Please add a power analysis to provide some justification for the sample size.
We cite the published power analysis from which we specified a recruitment goal of 80 (see Recruitment section on p. 9). We expected to enroll nearly 80 people from the chosen recruitment method. When we realized the inadequacy of this method, we implemented a trial-and-error approach that resulted in the development of a tailored recruitment strategy that seems promising for a future study.

E. Human subjects: please add “all participants provided written informed consent”
Added (p. 11).

Results
A. Report in greater detail on the recruitment methods, such as the length of time trying each method.
We have now noted that we began recruiting by mailing the 80 women who had participated in an earlier open-ended interview study by sending a letter inviting participation. Over approximately three months, 21 indicated a willingness to participate. Of these, 8 were eligible and 5 participated in the research trial. The other 7 participants were recruited through other methods. (pages 14-15)

B. Baseline demographics: Please add in the 6th person who withdrew from the study to the treatment group.
This data was not entered into the database and not easily accessible. If the reviewer insists, we could recall the data from storage and write a sentence in the results section, right after we note that she withdrew with no reason given and did not provide any additional data, along the following lines:
This [race], [employment status], [marital status], [age] year old woman had a baseline BFI of [fill], an income greater[less than] than $20,000, was [not] in severe pain, and [treatment history: had received chemotherapy but not radiation therapy or hormone therapy].

C. Please indicate (if true) that there was no statistically significant difference between either group based on sociodemographic or clinical indications. (Reviewer does not like current formulation: “There was no evidence that the randomization procedure failed to provide for a fair comparison between treatment and control in the relief of BFI-measured CRF.”)
The paper now states: “There were no statistically significant differences between the treatment (n=5) and control (n=7) subjects” (p. 15)

D. Add the mean age with standard deviation and some basic information about race/ethnicity and leave the rest to the table.
We added this information to Table 3. Overall, the mean age of study participants was about 54 and about two-thirds of the participants were white.

E. Indicate the mean difference between groups in BFI from baseline to end of study along with standard deviation (not error).
The standard deviations are now reported in Table 4.

F. Report the p-value from your model from the treatment variable and round off to the second decimal place.
The paper now indicates that regression model estimates indicate that the treatment group patients benefited from a 2.38-point greater decline in CRF compared to the control group (See Table 5). The standard error of the treatment variable was 1.35 and the p-value was 0.08.

Discussion

A. Rewrite the discussion to focus on the clinical trial (not the recruitment strategy).
We condensed the recruitment discussion to one paragraph. (see page 17-18)

B. Compare and contrast your results to other studies using exercise and acupuncture/acupressure (How is your study better, worse, etc.).
We have added several sentences in response to this comment:

Participants in the treatment group experienced a 66% reduction in fatigue. This result compares very favorably with similar studies examining acupuncture or acupressure in the relief of CRF.[18-22] We believe that a formal program of patient education integrated with acupuncture provides more benefit than acupuncture alone because it likely acts in a more broad-based manner and more fully incorporates the patient into the treatment plan. (page 17)

C. Add how well participants followed study suggestions in the treatment group.
We note in Table 1 the mechanism of assessment that we developed. (pages 31-33)

D. What are your study limitations?
We added a section on study limitations (see pages17-18).

E. Be specific as to what would be the next logical study to conduct and what this would entail.
We state:

In conclusion, this study provided evidence of feasibility for a larger-scale RCT on patient education integrated with acupuncture to relieve CRF. (page19)

Jun Mao Reviewer Report: Summary and Responses

Overall

A. Incomplete discussion of existing acupuncture/acupressure trials for fatigue literature. Cite these studies and contextualize your study with reference to them.
We have elaborated the introduction to discuss these studies and show the unique approach of our own study. (pages 6-8)

B. The discussion on recruitment is valuable but could be improved by authors showing the value of the waiting room recruitment method.
We have reworded the text to more clearly make the point that we did not compare the effectiveness of the recruitment strategies but instead drew upon our experience with the recruitment strategies to develop a tailored recruitment strategy.(see page 9)

C. Please discuss limitations of study.
We added a section on study limitations (pages17-18).
Specific comments
A. Suggests changing the title to something like “Integration of self-care education and acupuncture”
We have changed the title to:
“Patient education integrated with acupuncture for relieving cancer-related fatigue: Randomized controlled feasibility study”

B. Abstract: Change the results to conform to typical style for trial reporting.
We followed the advice so the text now reads:
“Compared to usual care control, the intervention was associated with a 2.38-point decline in the BFI (90% Confidence Interval of 0.586 to 5.014; p<0.10).”

C. Abstract conclusions should be changed to reflect the need for a strong recruitment method in subsequent trials.
We have changed the abstract to read:
“An effective recruitment strategy will be essential for the successful execution of a larger-scale trial.”

D. Introduction: Need to review the existing therapies to build a rationale for the study, show that it addresses an important gap, and is plausible.
We responded to this comment by rewriting the introduction (see pages 6-8).

E. Need to spell out BFI and HADS when they first appear.
We have now spelled out the acronyms the first time they appear (page 8):
measured by a score of 4 or greater on the Brief Fatigue Inventory (BFI).[18]…
The exclusion criteria were depression (Hospital Anxiety and Depression Score [HADS] depression score ( >10)

F. Interventions: explain in greater detail.
We expanded the section on interventions (pages 9-12).
It would have been possible to have had one acupuncturist do both the needling and the education, but we chose to separate this for reasons having to do with workflow (the acupuncturists were not dedicated researchers).

G. Provide justification for the sample size.
We cite the published power analysis from which we specified a recruitment goal of 80 (see Recruitment section on p. 9). We expected to enroll nearly 80 people from the chosen recruitment method. When we realized the inadequacy of this method, we implemented a trial-and-error approach that resulted in the development of a tailored recruitment strategy that seems promising for a future study.

H. The numbers for recruitment do not add up.
We corrected the typographic error so it now states that 5 people contacted the study team in response to a letter from the PI. (page 15)

I. Outcomes: It would strengthen the paper to add some relevant secondary outcomes.
We have added cognitive dysfunction outcomes (pages 13 and 16).

J. Authors need to make a better case that the waiting room recruitment strategy is more effective than the other strategies.
We have reworded the text to more clearly make the point that we did not compare the effectiveness of the recruitment strategies but instead drew upon our experience with the recruitment strategies to develop a tailored recruitment strategy (see page 9).

K. Please discuss how your work is similar or different from other acupuncture/acupressure/counseling alone trials.
We drew upon Social Cognitive Theory (SCT) and Integrative Medicine (IM) theory to integrate patient education and acupuncture. (see pages 16-17)

L. Please discuss the limitations of your study.
We have added a section on limitations (see pages 17-18).

M. Please note that successful recruitment strategies are needed for a larger trial.
We now state:
“In any case, thoughtful and proactive recruitment methods are needed for successful conduct of a larger trial.” (see page 18)

Additional Comments:

A. Abstract - Abstracts must be structured into Background, Methods, Results, Conclusions. Please remember to also update the Abstract details on the submission page.
We have now restructured the abstract in accordance with the journal requirement.

B. Trial registration - May I check whether the trial registration number for this study is NCT00646633? Please add the trial registration number to the abstract.
Yes, this is correct and we have added it to the abstract.

C. Ethical approval - Please include the details of the institutional review board(s) that approved the study.
We have provided additional details so that the text reads:
“General and cancer-specific review boards at UCLA approved this study (#06-010-01, #POP0504401) and all subjects consented to participate.”

D. Competing interests - Please include a “Competing interests” section Between the Conclusions and Authors Contributions. If there are none to declare, please write “The authors declare that they have no competing interests”.
We have added text indicating no competing interests.

E. Authors’ contributions
Please include an Authors contributions section after the section on competing interests.
We have added this section to the paper (page 20).