Author’s response to reviews

Title: Effects of Anma-massage therapy (Japanese massage) for gynecological cancer survivors: study protocol for a randomized controlled trial

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Author’s response to reviews: see over
Thank you very much for reviewing our paper and passing on the reviewer comments for our manuscript. We have revised our manuscript in accordance with all of the comments received, and provide a point-by-point response below.

In the manuscript, all revisions are indicated in blue.

We hope our manuscript is now judged suitable for publication.

We look forward to hearing from you in due course.

Sincerely,

Nozomi Donoyama

Editorial requests:

1) Please ensure the title conforms to journal style for study protocol articles. The title should follow the format "__________: study protocol for a randomized controlled trial."

[Answer]

We have changed the format of title as advised: Effects of Anma-massage therapy (Japanese massage) for gynecological cancer survivors: study protocol for a randomized controlled trial.

Handling Editor's comments:

"1) justify the use of multiple questionnaires with overlapping domains. For example, the HADS, the POMS and the EORTC all measure anxiety."

[Answer]

In the manuscript, we have added a brief explanation about what we would like to explore in this trial using four kinds of psychological scales.

The primary objective of this study is to verify the effects of continuous Anma-massage therapy on
the mind and body of cancer survivors. Therefore, based on previous studies, we decided to investigate its effects on the psychological aspects of i) anxiety and depression, ii) quality of life (QOL), and iii) coping style towards cancer. The reasons we have chosen to use the four scales are as follows.

i) Hospital Anxiety and Depression Scale (HADS)
The HADS was developed to measure anxiety and depression for cancer patients. It is known that cancer patients and cancer survivors are often anxious about recurrence and/or death even if treatment was completed and this causes them physical and psychological stress. Some studies have demonstrated that massage therapy is effective for reducing anxiety and depression, and our previous preliminary study [Ref. 16] showed that scores for anxiety measured by the State-Trait Anxiety Inventory (20 items) and depression measured by the Self-Rating Depression Scale (20 items) were lowered by Anma-massage therapy. Therefore, in the present study, to confirm such improvements in anxiety and depression, we chose the 14-item HADS to lower the burden of assessment on patients.

ii) European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30)
This scale was developed to measure QOL in cancer patients. The reliability and validity have been proved, and it has been used in many QOL studies involving cancer patients. In previous studies, QOL was improved by massage therapy. Therefore, to explore the improvement of QOL by Anma-massage therapy in the present study, we chose this scale. Its subscales concern global health status, functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning), and symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties).

iii) Adjustment to cancer (coping style for cancer)
Some studies report the correlation of adjustment to cancer, QOL, and mental health [Refs 21 and 22]. During massage sessions, some communication naturally occurs between the massage therapist and patient. Some change in the patient's coping style might occur through their communication. In our trial, change in psychological adjustment to cancer (coping style to cancer) is assessed using the questionnaire Measure of Adjustment to Cancer (MAC).

These three scales (HADS, EORTC QLQ-C30, and MAC) are valid scales which can be used to assess changes by long-term intervention.

Since the secondary objective in our trial is to confirm the immediate effects on the mind and body of a single Anma-massage session for cancer survivors, the fourth scale we chose is the Profile of Mood States-Brief Japanese Version (POMS). This scale is used in various interventional studies...
for assessing the immediate changes between pre- and post-intervention.

2) the primary analysis should be by ANCOVA (see Vickers and Altman BMJ 2001)"

[Answer]
Thank you very much for this comment. The journal paper provided (Vickers and Altman, *BMJ*, 2001) was very helpful to us when revising the manuscript. According to the paper, in the example concerning the data obtained for Shiatsu, we learned that it may be possible for bias to exist even with a randomized controlled trial design. Accordingly, we have changed the primary analysis to ANCOVA.
RESPONSE TO REVIEWER 1:  Antony J. Porcino

Thank you very much for the valuable review and for referring us to useful articles. We have revised the statistical analysis completely and small revisions were made elsewhere in the manuscript to address all the comments received. We recognize that need for us to study more on how to conduct clinical trials and we will reflect your valuable suggestions in our article that reports the results of this trial. Our detailed responses are given below.

1) This trial protocol is a mix of pragmatic and explanatory design choices on the pragmatic-explanatory continuum (for example of what this may look like, see PRECIS Thorpe 2009). The approach to many of those choices seem pragmatic in that they either address real-world issues or allow for comparison with other studies even if they are more explanatory (the cortisol measurements are a good example). The odd mix did, however, require time to reflect on how, what, and why the trial design was meant to accomplish, and I think additional information from the authors through a lens like PRECIS could help readers, interpreters/users of the results, and further trials on this subject.

[Answer]

Thank you for this suggestion. We will study PRECIS and other documents.

2) One particular concern regards the choice of a single practitioner to provide all treatment, without description of how that practitioner's treatment process, training, or experience compares with other providers. While this ensures (as the authors comment) very high internal validity, given the pragmatic nature of other protocol features, this particular design choice needs to be better explained in the context of the trial as a whole.

[Answer]

In terms of the practitioner's treatment process, the protocol of Anma-massage therapy in this trial will be the same as that used in our preliminary studies [Ref. 16, 19, 20]. We understand your concern. However, since patients will have different physical subjective symptoms, in order to assess the effectiveness of Anma-massage practice in a clinical setting, the therapist will treat their symptoms on an individual patient basis. In light of this, we decided to mention only the standard version of the massage procedure, which is no more than what was described in our preliminary studies and thus we referenced them in this manuscript.

When we write up the results of the trial after its completion, we will describe the massage procedure in detail, explaining the procedure the therapist followed for each patient. To address your point, we have added a small sentence about the therapist’s past works.

3) It is noted that a trial inclusion criteria is "Desire to receive Anma-massage therapy". The effects on the outcome of previous experience with Anma massage expectations regarding
Anma massage, and desire for the treatment have not been addressed in this protocol. I leave this as a "discretionary" revision only because in many research trials these issues are often not fully addressed or are considered to be addressed by the control group. However, it needs to be considered that they may constitute a significant component of the placebo or contextual component of the result. I do not consider this a wrong choice—it will help both with trial recruitment, and likely reflects real-world uptake of Anma massage should the results prove positive—but would indicate that the results will not reflect purely or only the effects of Anma massage. This issue is common in complementary and alternative medicine research, and may be helpful to the authors in placing their trial design and results in context (see, for example, Boulanger et al. 2012, The Development and Validation of the Client Expectations of Massage Scale).

[Answer]
Thank you for raising this important point.

Patients visit the coordinating office to receive an explanation about the trial and after the meeting, only people who understand and agree to receive Anma-massage are registered to the trial. Thus, the item of inclusion criteria, "Desire Anma-massage" is included in "Receipt of written informed consent to participate in the trial from the patient". We have revised to delete this item from the eligibility criteria in the manuscript.

We will change the eligibility criteria in our study protocol and apply the revised version of the study protocol to the Medical Ethics Committee of Tsukuba University of Technology to be approved as soon as possible.

4) New outcome tools have been added relative to the previous work these authors have done in the field, without clearly identifying the value of the outcome to the testing of the hypothesis, particularly as they relate to the (normal) use of these in massage trials.

[Answer]
We have newly added description of the primary endpoint in accordance with Reviewer 2's comment. Moreover, we have added brief explanations of the secondary endpoints following the Handling Editor's comment.

Specific questions to address:
1) 2)

[Answer]
We found the suggestions and implications you gave us very helpful to considering what we should study in our research, how we should analyze the obtained data, how we should write the research article upon completion of the trial, and how we manage further trials in general. We greatly
appreciate this advice.

3. Is the planned statistical analysis appropriate?
(a) The sample size calculation as explained is not clear as to the reasoning, given the expected effect sizes from the pilot studies.

[Answer]
We primarily set the sample size of this trial to be 14 patients per group, assuming that the mean VAS difference over the 2–month period is -20.8 (SD 19.6) in the Anma-massage group and remains unchanged in the no-Anma-massage (i.e. 0, and SD the same as that of the Anma-massage group, i.e. 19.6).

However, the assumption concerning the mean difference of in the no-Anma-massage group (i.e. 0) could be too optimistic, so we have added a sensitivity analysis to the assumption. This showed that a sample size of 30 participants per group is sufficient for most of the scenarios considered in the sensitivity analysis. We have added mention of this to the revised manuscript.

Additionally, while intention-to-treat analysis is proposed, the authors do not describe whether the sample size was adjusted to accommodate possible data loss or dropouts.

[Answer]
A sample size of 14 patients per group is sufficient to test these differences with 90% power. So a sample size of 30 patients per group would be enough to accommodate possible data loss or dropouts. We added mention of this to the manuscript:
"Therefore, the planned sample size will be 30 participants per group (60 participants in total). A sample size of 30 patients per group will also account for possible data loss or dropouts."

(b) "Pearson's Chi-squared test … will be used to test differences in categorical variables."

Given the use of t-tests for the parametric data, the Mann Whitney test or another non-parametric test (depends on which categorical variables) may be more appropriate to test differences rather than just discern that a difference exists.

[Answer]
The sentence “Pearson’s Chi-squared test … will be used to test differences in categorical variables” means that any binary or categorical (more than three levels) variables will be tested using Pearson’s Chi-squared test.

However, for continuous variables, including VAS score, we will first check the normality of the data, and if the data is not normally distributed, we will consider another analysis method such as the Mann-Whitney test. So have added the following sentence to the revised manuscript:
"A two-sample t-test or paired t-test will be used to detect differences in continuous variables. Pearson's chi-square test with continuity correction will be used to test differences in categorical variables. If these data are found not to be normally distributed, we will use in their place the Wilcoxon signed rank test or Mann-Whitney test, respectively."
RESPONSE TO REVIEWER 2: Myeong Soo Lee
http://www.trialsjournal.com/imedia/1570809201992901_comment.pdf

Thank you for giving me your valuable and useful comments. I answer your questions here and revised our manuscript as possible.

1. Please check the word counts for abstract. It looks like over 350.
   [Answer]
   The Abstract in the revised paper is 320/350 words.

2. page 6. 'Desire to receive Anma-massage therapy' means patients may have some expectation to receive Anma. This may discourage the control group and may give some effects on their response even though they will receive the Anma at the end of trial. I am not sure it is ethical or not. Do you have any solution to cover the possible discouragement for control group? They already know what Anma is. You cannot conceal the treatment.
   [Answer]
   We agree that the reviewer's point is a valid one.
   We created the design so that participants who are allocated to the control group can still receive a single Anma-massage session.
   When patients visit the coordinating office to receive an explanation about the trial, we are trying to give them understandable information verbally about just this point as well as refer to it in the written trial description. After the meeting, only people who understand and agree to this point are registered to the trial.

3. page 7. The effects of Anma may different according to type of cancer. Please consider this point when you do randomization. You can use stratification of cancer types. I don't agree 'Allocation adjustment factor....". You don't know what the factor is but you should consider this before doing trial.
   [Answer]
   We already started the trial in October 2012 under the protocol that allocation adjustment factors are not set in the trial due to insufficient evidence at present regarding what factors affect the effectiveness of Anma-massage therapy. We understand your point, but we decided on this point when considering allocation before beginning the trial. This is the first large-sample trial of Anma-massage therapy and there are few preliminary studies. Upon completion of this trial, something may be proven. We would like the trail design to stand for now, and if factors which affect the effectiveness of Anma-massage therapy are found through research or are suggested theoretically, we will consider them at the time of statistical analysis and discuss this issue in the research article that will follow the study.
4. What is a 40-min relaxing chat? Do you have any protocol for this? I think it is possible to give negative effects on the symptoms of cancer survivors e.g fatigue. Someone may have a stress for talking and so on. Is this reasonable to employ this control group for comparing Anma-massage? I recommend some relaxation instead of relaxation chat.

[Answer]
We understand your concern. Actually, we were seeking a suitable relaxation technique as a control intervention in our trial while developing the protocol. In our previous studies [Ref. 16, 19, 20], we used rest intervention in which the participants lay on the massage table without receiving massaging. However, in the clinical situation of Anma-massage therapy in Japan, patients usually enjoy talking with the massage therapist. Women especially talk a lot about their health and mental state and a massage therapist gives them full attention when talking, like a counselor. They divulge details about daily mental stress and what they enjoy. In light of this conventional practice in Japan, in this trial we decided that chatting for relaxation can serve as a control intervention, and named it "Relaxing chat" in the manuscript.

In our previous study for patients with Parkinson's disease (inwriting), using the relaxing chat as a control intervention the same as in this trial, endpoints of VAS for subjective complaints, hand movement functions, and gait functions were not changed. No negative or positive effects were seen as a result of having the relaxing chat.

5. It is unclear for primary endpoint. What is the severity of physical subjective complaints? The details may contains in secondary endpoints. Are there any difference between primary and secondary outcomes. Please make it clear what is the severity of physical subjective complaints.

[Answer]
We have added the method of how we assess the subjective complaints by using the visual analogue scale (VAS) to the manuscript. Moreover, we added explanation about what we measure using four kinds of questionnaire (secondary endpoints).

6. Why do author measure 3 points in experimenatal group and 4 points in control group?

[Answer]
This trial is a rare and is a valuable opportunity to confirm the effects of Anma-massage therapy. In addition, it is very hard to conduct such a trial, in terms of the recruitment of many patients, collaboration with a skillful massage therapist, medical doctors, and a statistician across different institutions, over the longer term, etc. Therefore, this trial incorporates many aspects we want to test out. We have two aims: to verify the effects of continuous Anma-massage therapy and to verify the effects of a single Anma-massage session. Thus, we chose this study design.
When patients visit the coordinating office to receive an explanation about the trial, we are trying to
give them understandable information verbally about just this point as well as refer to it in the
written trial description. After the meeting, only people who understand and agree to this point are
registered to the trial.

7. The statistical analysis is not clear. Please add how to compare the 3 points
values of experimental group with the 4 points values in control group.
[Answer]
We have explained which values are compared with which in the section on data collection, shown
in green letters. Moreover, we revised the method of statistical analysis following the Handling Editor's comment
2). Please also see the revised version of the section on statistical consideration.