

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Acupuncture Versus Massage for Pain in Patients Living with Advanced Cancer: A Protocol for the IMPACT Randomized Clinical Trial
<b>AUTHORS</b>	Romero, Sally; Emard, Nicholas; Baser, Raymond; Panageas, Katherine; MacLeod, Jodi; Walker, Desiree; Barton-Burke, Margaret; Liou, Kevin; Deng, G; Farrar, John; Xiao, Han; Mao, Jun; Epstein, Andrew

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Soo-Hyun Sung National Institute for Korean Medicine Development Seoul Branch, Department of Policy Development
<b>REVIEW RETURNED</b>	04-Dec-2021

<b>GENERAL COMMENTS</b>	<p>The authors present an study protocol of randomized controlled trial. The information is well-presented but some points must be improved.</p> <p>(Comment 1) I recommend authors to change protocol title. This protocol is not a study design comparing the integrative medicine group and the conventional medicine group. - e.g. "Integrative Medicine" -&gt; "Acupuncture" or "Complementary and Alternative Medicine"</p> <p>Methods and Analysis (Comment 2) Acupuncture and massage are completely different types of intervention. Therefore, strict blinding is required. Blinding method of outcome evaluators and participants should be supplemented.</p> <p>(Comment 3) I recommend authors to supplement monitoring system on side effects for each participant according to the Common Terminology Criteria for Adverse Events (CTCAE)</p> <p>(Comment 4) Authors mentioned manual with the specific treatment protocols for acupuncture and massage. (pg 11 line 54-56) I recommend authors to add the manual as a supplementary file. This manual will guarantee the same procedure.</p>
-------------------------	--

<b>REVIEWER</b>	Gary Asher University of North Carolina, Family Medicine
<b>REVIEW RETURNED</b>	08-Feb-2022

<b>GENERAL COMMENTS</b>	This is a study protocol for an RCT of the comparative effectiveness of acupuncture versus massage for musculoskeletal pain in
-------------------------	--

	<p>advanced cancer patients. Overall, the manuscript is very well written, and the rationale and methods are very clearly described. The results of this trial will be helpful for patients and providers to make informed decisions regarding management of cancer pain. I have no major comments or recommendations for revision. A few minor comments are noted below.</p> <p>1) Is there any information on the use of the METE for expectancy regarding massage? I believe this may be an acupuncture-specific tool and some additional information may help readers understand its applicability to massage.</p> <p>2) I suspect in the study protocol there is a process for evaluating harms of both interventions. Even if there will not be a formal analysis of harms, it would be beneficial for study investigators to describe how harms information will be gathered and assessed.</p> <p>3) For Aim 2 – Consider including additional information on which groups will be included in subgroup analyses and how many subgroup analyses will be conducted along with any procedures to manage multiple testing. Also, consider prespecifying anticipated direction of effects for subgroup analyses.</p> <p>4) Section 2.12 sample size – consider adding information on justification for 20% dropout (presumably based on prior experience of this group).</p>
--	---

### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Soo-Hyun Sung, National Institute for Korean Medicine Development Seoul Branch

Comments to the Author:

The authors present an study protocol of randomized controlled trial. The information is well-presented but some points must be improved.

(Comment 1) I recommend authors to change protocol title. This protocol is not a study design comparing the integrative medicine group and the conventional medicine group.

- e.g. "Integrative Medicine" -> "Acupuncture" or "Complementary and Alternative Medicine"

Response: Thank you for this recommendation. We have updated the protocol title per this suggestion to: "Acupuncture Versus Massage for Pain in Patients Living with Advanced Cancer: A Protocol for the IMPACT Randomized Clinical Trial."

Methods and Analysis

(Comment 2) Acupuncture and massage are completely different types of intervention. Therefore, strict blinding is required. Blinding method of outcome evaluators and participants should be supplemented.

Response: We agree and thank you for this suggestion. We have updated Section 2.5 of the manuscript (page 7) to include blinding information: "Given the nature of the interventions, patients and providers will not be blinded to treatment assignments. The PI, study statisticians, and outcome assessment clinical research coordinator will be blinded to treatment assignments."

(Comment 3) I recommend authors to supplement monitoring system on side effects for each participant according to the Common Terminology Criteria for Adverse Events (CTCAE)

Response: Thank you for this recommendation. We have added the following language to Section 2.10 of the manuscript (page 11): "Patients will be monitored for side effects at each visit. Adverse

effects related to the administration of either acupuncture or massage will be collected each week before and after each treatment by the acupuncturist/massage therapist or clinical research coordinator. The Common Terminology Criteria for Adverse Events (CTCAE) Version 5 will be utilized for toxicity evaluation.”

(Comment 4) Authors mentioned manual with the specific treatment protocols for acupuncture and massage. (pg 11 line 54-56) I recommend authors to add the manual as a supplementary file. This manual will guarantee the same procedure.

Response: As requested, we have added specific treatment protocols for acupuncture and massage as supplementary files.

Reviewer: 2

Dr. Gary Asher, University of North Carolina

Comments to the Author:

This is a study protocol for an RCT of the comparative effectiveness of acupuncture versus massage for musculoskeletal pain in advanced cancer patients. Overall, the manuscript is very well written, and the rationale and methods are very clearly described. The results of this trial will be helpful for patients and providers to make informed decisions regarding management of cancer pain. I have no major comments or recommendations for revision. A few minor comments are noted below.

1) Is there any information on the use of the METE for expectancy regarding massage? I believe this may be an acupuncture-specific tool and some additional information may help readers understand its applicability to massage.

Response: Thank you for this helpful suggestion. The METE has been adapted from the Acupuncture Expectancy Scale to include other interventions such as herbal treatment or cognitive behavioral therapies. We have included this information and references to Section 2.8 of the manuscript.

2) I suspect in the study protocol there is a process for evaluating harms of both interventions. Even if there will not be a formal analysis of harms, it would be beneficial for study investigators to describe how harms information will be gathered and assessed.

Response: Thank you for this recommendation. As stated above for Reviewer #1, we have added additional language on how side effects and adverse events will be monitored throughout the trial to Section 2.10 of the manuscript (page 11).

3) For Aim 2 – Consider including additional information on which groups will be included in subgroup analyses and how many subgroup analyses will be conducted along with any procedures to manage multiple testing. Also, consider prespecifying anticipated direction of effects for subgroup analyses.

Response: As requested, we have added additional information regarding subgroup analyses to Section 2.11, Aim 2 of the manuscript (page 12). It is important to point out that this type of subgroup analyses are hypotheses generating and exploratory and cannot replace the primary analyses.

4) Section 2.12 sample size – consider adding information on justification for 20% dropout (presumably based on prior experience of this group).

Response: We appreciate this suggestion and have added more information regarding our justification for 20% dropout to Section 2.12 of the manuscript (page 13): “Based on our prior

experience and given that patients living with advanced cancer may have unanticipated health issues (e.g., hospitalizations, death), we conservatively anticipate loss to follow up to be 20% by 26 weeks.”

Thank you again for the opportunity to revise our manuscript. The peer review process has strengthened the manuscript. Please feel free to contact me with any questions at maoj@mskcc.org or 646.608.8552. I look forward to hearing from you.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Soo-Hyun Sung National Institute for Korean Medicine Development Seoul Branch, Department of Policy Development
<b>REVIEW RETURNED</b>	14-May-2022
<b>GENERAL COMMENTS</b>	After reviewing the author responses, the author successfully addressed most of the comments and suggestions.
<b>REVIEWER</b>	Gary Asher University of North Carolina, Family Medicine
<b>REVIEW RETURNED</b>	28-Apr-2022
<b>GENERAL COMMENTS</b>	Thank you for the revisions of this manuscript, which are well done. I have no further comments. I look forward to seeing the results of this trial in the future.