PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	USE OF IMMPACT DOMAINS IN CLINICAL TRIALS OF ACUPUNCTURE FOR CHRONIC PAIN: A PROTOCOL FOR A METHODOLOGICAL SURVEY
AUTHORS	Mazzei, Lauren; Bergamaschi, Cristiane; Silva, Marcus; Lopes, Luciane

VERSION 1 – REVIEW

REVIEWER	Hamid R Baradaran Iran University of Medical Sciences, Tehran, Iran I have no conflict of interest
REVIEW RETURNED	11-Jan-2017

GENERAL COMMENTS	1-Introduction is long please make it shorter 2- Why is time limited ? 3- Please consider the verb in sentences !! If this SR-MA wants to be carried out , or performed already ?!!

REVIEWER	Paul Vaucher University of Applied Sciences and Art Western Switzerland (HES-SO), Switzerland
REVIEW RETURNED	17-Apr-2017

GENERAL COMMENTS	Thank you for having me review your protocol. I hope my comments will be useful to improve your manuscript. Overall, the rationals for running your study are relevant and up-to-date. Were I had more difficulties was truly understanding what you were trying to do. I did not find it very clear whether you wanted to run a systematic review to evaluate effects of acupuncture on chronic pain using recommended outcomes from the IMMPACT statement or whether you wanted to assess the methodological quality of outcome reporting in published trials on the subject. I also was unable to assess your statistical methodology given I was unable to understand what method was used to assess which research question. I think adding a section with research questions would make things easier for the reader. Here are a few questions and comments I came up with during the review:

	1. When choosing research terms, are you sensitive enough when only using one term for chronic pain? Would it not be better to also add other terms such as "persistent pain", "pain AND chronicity"? 2. If you are considering citation tracking, it could be useful to also track citations forwards. This can be done by searching articles that have cited the articles you have retained. 3. I do not understand your time-frame. Why are you excluding studies that have being published after 2010? 4. Why are your exclusion criteria for health conditions only provide restrictions for neck and shoulder pain but not for other conditions (ex. headache, bellyache, low back pain, etc.)? 5. I am unable to assess your statistical methods given I do not understand which approach is meant to answer which question. It would make things much easier if you would structure your protocole by clearly formulating questions at the start and then following the same order when describing your statistical methods. 6. I would avoid using sentences and repetitions such as "We will perform logistic regression adjusted to analysis and hypothesis.", "We are to carry out logistic regressions adjusted to the analysis and hypothesis". 7. Please specify your hypothesis and what predictors you want to take into consideration. Avoid using generic sentences such as "Multicollinearity tests will examine whether any predictors were correlational".

REVIEWER	Shiyan Yan China Academy of Chinese Medical Sciences China
REVIEW RETURNED	24-Apr-2017

GENERAL COMMENTS	1. The following statement in Statistical Analysis section was repeated. "We are to carry out logistic regressions adjusted to the analysis and hypothesis. The associations with the biggest IMMPACT domains are: (1) the latest published trials, (2) trials published in the strongest impact journals, and (3) trials which started recruiting participants one year after the publication of IMMPACT recommendations." 2. Please list all your planed analyses and describe the statistical methods with enough detail. 3. “We will perform logistic regression adjusted to analysis and hypothesis”, what is your hypothesis? Does it refer to “The associations with the highest IMMPACT domain rates are: (1) The latest published trials, (2) Trials published in the strongest impact journals, and (3) Trials that started recruiting participants a year after the publication of IMMPACT recommendations.”? Please list all factors included in the model. 4. Specify in the statistical analysis section the statistical software version, manufacturer.

REVIEWER	Qianyun Chai China Academy of Chinese medical sciences
REVIEW RETURNED	28-Apr-2017

GENERAL COMMENTS	This study is an interesting survey that the authors want to check whether the researchers have used the IMMPACT

	recommendations in measuring CRCT-NOCP outcomes. However, what does the “methodology” mean, and what does this study mean may need a deeply stated. 1. The description of the objective seem to be a clinical survey, however, it is most like a literature study, or an assessment of original research method. 2. The recruited number of patients equal or less than 100 are mentioned in Summary Method part, but recruited number of patients change to equal or more than 100 in Study Eligibility Criteria part, which one is right and why?. 3. What is the purpose of using the Cochrane risk of bias? 4. How do you use the result of IMMPACT, giving the score? And why are you use the regression analysis, the purpose might be stated in the Objective part.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Thank you. We do appreciate your suggestions.

- C1. Introduction is long please make it shorter.

R1. We´ve made changing in introduction to become shorter.

- C2. 2- Why is time limited?

R2. We will carry out this methodological survey since a systematic review already published in a core journal (Vickers et al.). We will update their searching and will include new RCTs using the same criteria.

- C3. Please consider the verb in sentences!! If this SR-MA wants to be carried out, or performed already?!!

R3. Thank you. We´ve made changed in the verbs.

Reviewer 2

General comments

Dear Authors,

- C1. Thank you for having me review your protocol. I hope my comments will be useful to improve your manuscript. Overall, the rationals for running your study are relevant and up-to-date.

R1. Thank you for your questions and suggestions. This will help us to improve this protocol.

- C2. Where I had more difficulties was truly understanding what you were trying to do. I did not find it very clear whether you wanted to run a systematic review to evaluate effects of acupuncture on chronic pain using recommended outcomes from the IMMPACT statement or whether you wanted to assess the methodological quality of outcome reporting in published trials on the subject.

R2. Sorry, we´ve checked the objective again to make it clear. We´ve stated as follow:

The main objective of this study is to check whether methodological quality of outcome reporting in published, trials have used IMMPACT recommendations in measuring CRCT-NOCP outcomes when acupuncture was used as a treatment.

- C3.I also was unable to assess your statistical methodology given I was unable to understand what method was used to assess which research question. I think adding a section with research questions would make things easier for the reader.

R3. Thanks. We´ve made changing in section statistical analysis to make this item clear.

Here are a few questions and comments I came up with during the review.

Please see below our response to each one.

- C4. When choosing research terms, are you sensitive enough when only using one term for chronic pain? Would it not be better to also add other terms such as "persistent pain", "pain AND chronicity"?

R4. We use the same terms as the previous SR. The term “chronic pain” as a MESH term include all of the words you are mentioning.

- C5. If you are considering citation tracking, it could be useful to also track citations forwards. This can be done by searching articles that have cited the articles you have retained.

R5. Thanks for the suggestion.

- C6. I do not understand your time-frame. Why are you excluding studies that have being published after 2010?

R6. We will use clinical trials published since 2004 that were included in the systematic review already published by Vickers et al., and we will update this prior searching including trials published nowadays. We will not exclude trials after 2010. Please, have a look in sections methods. We made this part as clear as possible.

- C7. Why are your exclusion criteria for health conditions only provide restrictions for neck and shoulder pain but not for other conditions (ex. headache, bellyache, low back pain, etc.)?

R7. Thank you. We´ve reviewed it.

- C8. I am unable to assess your statistical methods given I do not understand which approach is meant to answer which question. It would make things much easier if you would structure your protocol by clearly formulating questions at the start and then following the same order when describing your statistical methods.

R8. Thanks. We´ve made changing in section statistical analysis to make this item clear.

- C9. I would avoid using sentences and repetitions such as "We will perform logistic regression adjusted to analysis and hypothesis.", "We are to carry out logistic regressions adjusted to the analysis and hypothesis".

R9. Thanks. We´ve made changing in section statistical analysis to make this item clear.

- C10. Please specify your hypothesis and what predictors you want to take into consideration. Avoid using generic sentences such as "Multicollinearity tests will examine whether any predictors were correlational".

R10. Thanks. We´ve made changing in section statistical analysis to make this item clear.

Reviewer 3

- C1. The following statement in Statistical Analysis section was repeated. "We are to carry out logistic regressions adjusted to the analysis and hypothesis. The associations with the biggest IMMPACT domains are: (1) the latest published trials, (2) trials published in the strongest impact journals, and (3) trials which started recruiting participants one year after the publication of IMMPACT recommendations."

R1. Thanks. We´ve made changing in section statistical analysis to make this item clear.

- C2. Please list all your planed analyses and describe the statistical methods with enough detail.

R2. Thanks. We´ve made changing in section statistical analysis to make this item clear.

- C3. “We will perform logistic regression adjusted to analysis and hypothesis”, what is your hypothesis? Does it refer to “The associations with the highest IMMPACT domain rates are: (1) The latest published trials, (2) Trials published in the strongest impact journals, and (3) Trials that started recruiting participants a year after the publication of IMMPACT recommendations.”? Please list all factors included in the model.

R3. Thanks. We´ve made changing in section statistical analysis to make this item clear.

- C4. Specify in the statistical analysis section the statistical software version, manufacturer.

R4. All calculations will be performed in STATA 14.2. Thanks. We´ve made changing in section statistical analysis to make this item clear.

Reviewer 4

General comments

- C1. This study is an interesting survey that the authors want to check whether the researchers have used the IMMPACT recommendations in measuring CRCT-NOCP outcomes.

R1. We would like to thank you for the important suggestions to our research.

- C2. However, what does the “methodology” mean, and what does this study mean may need a deeply stated. The description of the objective seems to be a clinical survey, however, it is most like a literature study, or an assessment of original research method.

R2. This is a methodological study. We are not checking effects of acupuncture on chronic pain. The main objective of this study is to check whether methodological quality of outcome reporting in published trials, have used IMMPACT recommendations in measuring CRCT-NOCP outcomes when acupuncture was used as a treatment. We´ve made changing in this part in the paper as you can see.

- C3. The recruited number of patients equal or less than 100 are mentioned in Summary Method part, but recruited number of patients change to equal or more than 100 in Study Eligibility Criteria part, which one is right and why?

R3. Thank you. Considering there are many studies about chronic pain and acupuncture we´ve decided select only those with greatest number of patients , as Vickers et al., already used in theirs SR. We´ve made correction (≥ 100 pts).

- C4. What is the purpose of using the Cochrane risk of bias?

R4. It is a well-established tool to measure Risk of Bias and check the quality of RCTs selected.

- C5. How do you use the result of IMMPACT, giving the score? And why are you use the regression analysis, the purpose might be stated in the Objective part.

R5. We´ve made changing in section statistical analysis to make this item clear.

VERSION 2 – REVIEW

REVIEWER	Paul Vaucher University of Applied Science Western Switzerland (HES-SO), Switzerland
REVIEW RETURNED	02-Jun-2017

GENERAL COMMENTS	This revised version is much clearer than the previous manuscript and authors have managed to improve it considerably. There are a few remaining gaps that should be quite easy to bridge. 1. I still think a section that clearly states the research questions under investigation is necessary. This would improve the protocol and prevent aligning future questions to results rather than the opposite. It does seem important to report the study objective consistently. The objective in the summary and introduction are not the same as the ones planned for the analysis which is also different to the one stated in the discussion. There seems to be some confusion on whether the study only aims to quantify the proportion of studies that are now using IMMPACT outcomes or whether it wishes to measure the added value of having used these outcomes or even the efficiency of acupuncture when using IMMPACT outcomes. If all these are study objectives, this should be clearly addressed and statistical approaches to address each of them should be made clear. 2. The search string has been made clear and the use of MeSH related terms is now evident. 3. When assessing study quality, it is not clear why you are using a modified method rather than a standard appraisal tool. 4. The description in statistical analysis as been made much clearer. For the bootstrapping methods in the sensitivity analysis, it would nevertheless be worthwhile to mention what bootstrapping is intended for (ex. internal validity of the model, replacing missing data). It would also be useful to provide some indications on the critical number of studies that need to be included for the statistical analysis to be made. You are not running a classical meta-analysis but are trying to evaluate the added value of using IMMPACT outcomes rather than other outcomes after adjusting for other factors. 5. It would be relevant to give precision on what factors you think putting into your model to test whether using IMMPACT outcomes could influence results. You might also want to give details on how you intend to standardise measures across different scales and measuring methods (e.i. effect size). 6. There are a few typos meaning the text still does need some editing (ex. “IN Brésil” and “In caseof”). 7. In the discussion, it is still confusing whether your review will provide indication on the added value of using IMMPACT outcomes rather than other outcomes or provide evidence on the efficiency of acupuncture on persistent pain. Having a consistent message on your intent seems important and the discussion should be revised in consequence.

	8. I would also appreciate a small paragraph on risks and ways to overcome them if they were to occur. Three important risks I can think of is heterogeneity between the studies making it impossible to pool data and model the added value of IMMPACT outcomes, not having enough studies to be able to infer differences in use of outcomes, and residual confounding.

REVIEWER	Shiyan Yan Institute of Clinical Basic Medicine China Academy of Chinese Medical Sciences China
REVIEW RETURNED	07-Jun-2017

GENERAL COMMENTS	1. The second paragraph of 'statistical analysis' section, the author said "It is also planned to quantify the number of IMMPACT domains that will be served, in order to generate a score between 0-4 points.", please give the definition of the score from 0 to 4. 2. "Sensitivity analysis will be performed by means of a bootstrap technique.", which outcomes will need to conduct sensitivity analysis? 3. The author said "The general aim of this project is to verify changes occurred in the way of reporting and assessing outcomes after the publication of IMMPACT recommendations in CRCT about the use of acupuncture in patients with NOCP." This seems to not consist with the statistical analysis. If the aim is to explore the changes of reporting and assessing outcomes after the publication of IMMPACT, the statistical analysis need focus on the comparison of the reporting situation of IMMPACT before and after its publication. And the inclusion of RCT also need be adjusted according to your general aim. 4. Please remove the sentence "A regression analysis will be conducted to explore factors that may be associated with the presence of outcome domains according to IMMPACT recommendations." From Data Extraction section. 5. "Factors associated with the IMMPACT score will also be investigated. Depending on the data distribution, analysis of variance (ANOVA) or Kruskal Wallis will be performed." Which outcomes will be analyzed by ANOVA or Kruskal Wallis test?

VERSION 2 – AUTHOR RESPONSE

C1. This revised version is much clearer than the previous manuscript and authors have managed to improve it considerably. There are a few remaining gaps that should be quite easy to bridge.
R1. Thank you. We do appreciate your suggestions.

C2.1. I still think a section that clearly states the research questions under investigation is necessary. This would improve the protocol and prevent aligning future questions to results rather than the opposite.
R2.1. Thank you. We added it.

C2.2. It does seem important to report the study objective consistently. The objective in the summary and introduction are not the same as the ones planned for the analysis which is also different to the

one stated in the discussion.
R2.2. The objectives of the abstract, introduction and discussion have been aligned. Thank you for your notes.

C2.3. There seems to be some confusion on whether the study only aims to quantify the proportion of studies that are now using IMMPACT outcomes or whether it wishes to measure the added value of having used these outcomes or even the efficiency of acupuncture when using IMMPACT outcomes. If all these are study objectives, this should be clearly addressed and statistical approaches to address each of them should be made clear.
R2.3. We made this clearly as follow: The statistical analyzes carried out in this survey will aim to identify the factors associated with the change in reporting or adherence to the IMMPACT recommendations, in RCT made since its publication.

C3. The search string has been made clear and the use of MeSH related terms is now evident.
R3. Thank you.

C4. When assessing study quality, it is not clear why you are using a modified method rather than a standard appraisal tool.
R4. The percentage of unclear response using the cochrane's standard method is high, making it a difficult interpreting tool for clinicians. Two studies have shown that in RCT specific instructions for estimating the quality of such works are valid and reliable.

C5.1. The description in statistical analysis as been made much clearer.
R5.1. Your previous notes have helped us. Thank you.

C5.2. For the bootstrapping methods in the sensitivity analysis, it would nevertheless be worthwhile to mention what bootstrapping is intended for (ex. internal validity of the model, replacing missing data). It would also be useful to provide some indications on the critical number of studies that need to be included for the statistical analysis to be made. You are not running a classical meta-analysis but are trying to evaluate the added value of using IMMPACT outcomes rather than other outcomes after adjusting for other factors.
R5.2. We describe in greater detail the use of bootstrap and logistic regression.

C6. It would be relevant to give precision on what factors you think putting into your model to test whether using IMMPACT outcomes could influence results. You might also want to give details on how you intend to standardise measures across different scales and measuring methods (e.i. effect size).
R6. The factors were detailed in the statistical analysis session as well as the measurement methods.

C7. There are a few typos meaning the text still does need some editing (ex. “IN Brésil” and “In caseof”).
R7. The terms have been revised. Thank you.

C8. In the discussion, it is still confusing whether your review will provide indication on the added value of using IMMPACT outcomes rather than other outcomes or provide evidence on the efficiency of acupuncture on persistent pain. Having a consistent message on your intent seems important and the discussion should be revised in consequence.
R8. As previous note, the objective in the discussion has been aligned with the other sections of the text, and our intention is now clearer.

C9. I would also appreciate a small paragraph on risks and ways to overcome them if they were to occur. Three important risks I can think of is heterogeneity between the studies making it impossible to pool data and model the added value of IMMPACT outcomes, not having enough studies to be able to infer differences in use of outcomes, and residual confounding.
R9. Sorry. We didn´t follow your thoughts. We don´t intent to pool data in the survey methodological.

Reviewer 3

C1. The second paragraph of 'statistical analysis' section, the author said "It is also planned to quantify the number of IMMPACT domains that will be served, in order to generate a score between 0-4 points.", please give the definition of the score from 0 to 4.
R1. We appreciate the suggestion and include the description of the score in the statistical analysis session.

C2. "Sensitivity analysis will be performed by means of a bootstrap technique", which outcomes will need to conduct sensitivity analysis?
R2. We added the information as follow: For all calculations, sensitivity analyzes will be performed.

C3. The author said "The general aim of this project is to verify changes occurred in the way of reporting and assessing outcomes after the publication of IMMPACT recommendations in CRCT about the use of acupuncture in patients with NOCP."

This seems to not consist with the statistical analysis. If the aim is to explore the changes of reporting and assessing outcomes after the publication of IMMPACT, the statistical analysis need focus on the comparison of the reporting situation of IMMPACT before and after its publication. And the inclusion of RCT also need be adjusted according to your general aim.
R3. The objectives of the abstract, introduction and discussion have been aligned. Thank you for your notes.

C4. Please remove the sentence "A regression analysis will be conducted to explore factors that may be associated with the presence of outcome domains according to IMMPACT recommendations." From Data Extraction section.
R4. Regressions are valid only when there is a minimum of 10 references. In our study, considering all RCT already (n= 31) included in Vickers et al. (2012) we will include the new ones after 2010.

C5. "Factors associated with the IMMPACT score will also be investigated. Depending on the data distribution, analysis of variance (ANOVA) or Kruskal Wallis will be performed." Which outcomes will be analyzed by ANOVA or Kruskal Wallis test?
R5. Depends on the distribution of the IMMPACT score. When the data is close to normal, analysis of variance (ANOVA) will be performed. When it is not normal data, Kruskal Wallis will be used.

VERSION 3 – REVIEW

REVIEWER	Paul Vaucher HES University of Applied Sciences Western Switzerland, Switzerland
REVIEW RETURNED	26-Jun-2017

GENERAL COMMENTS	This third version addresses all issues in the past versions and seems to provide sufficient details for the protocol to be reproduced.

REVIEWER	Shiyan Yan Institute of Clinical Basic Medicine China Academy of Chinese Medical Sciences
REVIEW RETURNED	11-Jul-2017

GENERAL COMMENTS	1.Please remove "the change in" from the first paragraph of statistical analysis section. 2.In the statistical analysis section, you mentioned that "For a good regression analysis, a minimum of 10 references is necessary, which will not be a problem since we will include previous SR studies." What is SR studies? 2.Plese give the statistical analyses conducted in the study were one sided test or two sided test. 3. Sensitivity analyses are not necessary in this study. 4.the statement -"Thereafter, for each domain, the measurement method is quantized, that is, whether the pain was measured by VAS and / or VAN, whether physical function was measured by multidimensional inventory to pain and / or inventory summary of the pain, whether the emotional state was measured by the Beck depression inventory and / or mood state profile, and whether the improvement in patient satisfaction was measured by the patient's overall impression of change. The correct applicability of the instrument will also be quantified (if the domain report was executed by the patient, clinical or third parties)." should be moved from statistical analyses section to "Definitions of IMMPACT outcome domain". Because these qualified methods are defined by IMMPACT, not by this study.

VERSION 3 – AUTHOR RESPONSE

Reviewer 2

C1. This third version addresses all issues in the past versions and seems to provide sufficient details for the protocol to be reproduced.
R1. Thank you. We do appreciate your suggestions.

Reviewer 3

C1. Please remove "the change in" from the first paragraph of statistical analysis section.
R1. The sentence has been removed. Thank you for your contributions.

C2. In the statistical analysis section, you mentioned that "For a good regression analysis, a minimum of 10 references is necessary, which will not be a problem since we will include previous SR studies." What is SR studies?
R2. These are the studies included in the systematic review (SR) that we use as reference, measured in the first sentence of the Reference Sources and Search

C3. Please give the statistical analyses conducted in the study were one sided test or two sided test.
R3. We will add this information in the statistical analysis session to make the manuscript clearer. Thanks for the suggestion.

C4. Sensitivity analyses are not necessary in this study.
R4. We agree with it.

C5. the statement -"Thereafter, for each domain, the measurement method is quantized, that is, whether the pain was measured by VAS and / or VAN, whether physical function was measured by multidimensional inventory to pain and / or inventory summary of the pain, whether the emotional state was measured by the Beck depression inventory and / or mood state profile, and whether the improvement in patient satisfaction was measured by the patient's overall impression of change.

The correct applicability of the instrument will also be quantified (if the domain report was executed by the patient, clinical or third parties)." should be moved from statistical analyses section to "Definitions of IMMPACT outcome domain". Because these qualified methods are defined by IMMPACT, not by this study.
R5. The statement was moved to the indicated section, making the manuscript clearer. Thanks for your suggestion.

VERSION 4 – REVIEW

REVIEWER	Shiyan Yan Institute of Clinical Basic Medicine China Academy of Chinese Medical Sciences
REVIEW RETURNED	10-Aug-2017

GENERAL COMMENTS	Please use the statement "Depending on the data distribution,analysis of variance (ANOVA) or Kruskal Wallis will be performed. All analyses were 2-sided tests at a significance level of 0.05." to replace "Depending on the data distribution, one-tailed analysis of variance (ANOVA) or one-tailed Kruskal Wallis will be performed. A significant statistical difference will be attributed to cases of p ≤0.05."

VERSION 4 – AUTHOR RESPONSE

C1. Please use the statement "Depending on the data distribution,analysis of variance (ANOVA) or Kruskal Wallis will be performed. All analyses were 2-sided tests at a significance level of 0.05." to replace "Depending on the data distribution, one-tailed analysis of variance (ANOVA) or one-tailed Kruskal Wallis will be performed. A significant statistical difference will be attributed to cases of p ≤0.05."
R1. The sentence was replaced as suggested. Thank you for your contributions.