Author’s response to reviews

Title: Predictors of the effects of treatment for shoulder pain: Protocol of an individual participant data meta-analysis

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Response to feedback

Dear Editor,

We would like to thank you and the peer reviewers for their helpful comments and suggestions with our protocol paper. Below, we respond to each of the reviewers’ comments and explaining all changes made to the manuscript.

Reviewer #1

The authors plan to conduct an individual participant data (IPD) meta-analysis of trials to evaluate the predictors of the effect of commonly used treatment strategies for shoulder pain. The authors have done previous work in this area and outcome measures they propose include shoulder pain intensity and function. The authors propose using a one-stage IPD meta-analysis to examine the effect of treatment-predictor interaction on outcome for each of the candidate predictors and assess for subgroup effects. Sensitivity analyses will include a two-stage meta-analysis. The authors have appropriately registered this protocol in the PROSPERO database.

The protocol is well written and statistical approaches seem appropriate.

(1) Indeed, an IPD meta-analysis addresses most of the limitations of aggregate data such as inconsistent definitions of some data and allows more detailed statistical analyses and a consistent approach to pooling. My main concern is how do the authors propose to standardize the data to enhance a consistent approach to the pooling, given that the intervention/control arms and outcome measures are not consistent across trials?

Response: We can only fully understand differences in outcome definitions and covariate coding once the IPD are obtained. For example, sometimes multiple outcomes are available in the IPD, but were not reported in the original trial publication. Where possible we will seek to avoid standardisation, and utilise the original scales of outcomes and candidate predictors that are reported. If we can convert or re-code certain outcomes or variables to ensure closer compatibility across studies, then we will also do this.

However, as correctly noted by the reviewer, if important differences still remain across studies once the IPD are obtained and inspected, we will seek to standardise scales for outcomes and predictor measurement. For example, continuous outcomes will be converted to a standardised
(for example, N(0,1)) scale in each study, by subtracting individual outcome values by the mean in the same study and then dividing by the standard deviation of values across individuals in the same study.

We have clarified this in the revised manuscript (page 14, line 19 - page 15, line 3).

(2) In their first objective, the authors state that "To estimate the overall effects of these four treatments, when compared to a control intervention (no treatment, advice and analgesics only; or sham), or when directly compared against each other". Are the authors proposing to lump these four treatments as one intervention? Corticosteroid injection, physiotherapy-led exercise, psychological treatments, and surgical interventions are different treatment strategies and even within each of these strategies, there are different interventions. The authors will need to clarify this properly.

Response: Thanks for this comment, we now realise we have not clearly explained the overall aim of this IPD meta-analysis, which is to provide evidence to improve decisions regarding different types of treatment for shoulder pain. Clinicians involved in the management of shoulder pain often have to decide which treatment is most suitable for which (subgroup of) patients, based on (diagnostic and prognostic) information obtained during their clinical assessment. We will therefore not lump all interventions together, as this would not address the question regarding what treatment is likely to be most effective for whom.

We will first estimate overall treatment effects for each of the four types of interventions separately, compared to a control. We will then estimate relative treatment effects when these interventions are directly compared against each other in pragmatic trials, prioritising comparisons that reflect decisions that are commonly made in the management of shoulder pain (e.g. corticosteroid injection versus physiotherapy-led exercise; surgical intervention versus exercise). Finally, for each of these comparisons separately, we will estimate treatment-predictor interactions for a number of a priori defined patient or disease characteristics, and describe relevant subgroup effects when interactions are detected.

In the revised manuscript, we have more clearly introduced the aim of the IPD meta-analysis, and clarified the (now three) objectives (abstract, pages 5, 6, and 7).

(3) The authors state "Attempts will be made to convert variables to the same scale for all studies." This also needs to be expanded upon.

Response: As mentioned in our response to comment 1 by this reviewer, if important differences still remain across studies once the IPD are obtained and inspected, we will seek to standardise scales for outcomes and predictor measurement. For example, if measured differently,
continuous variables will be converted to a standardised (e.g. N(0,1)) scale in each study, by subtracting individual values by the mean in the same study and then dividing by the standard deviation of values across individuals in the same study (see page 14, line 19 – page 15, line 3).

(4) Have there been any initial contact with potential investigators and if they will be willing to share their data? This is very relevant and needs to be clarified. How many investigators have agreed to share their data?

Response: Searches have been conducted, identifying 38 eligible trials. We are in the process of contacting authors, agreeing their participation, and transferring datasets. So far, we have been able to contact 31 trial author teams, of whom 26 have indicated their willingness to participate (datasets are no longer available or there are issues in terms of ethical approval for the other 5 trials). Data sharing agreements have been completed for 20 trials and data have been transferred for most of these. As this process is still ongoing we will report on this once finalised, when reporting the results of this IPD meta-analysis.

(5) Are there plans to contact investigators for unpublished data and any ethical approval issues involved?

Response: We will contact investigators to ask if they have any additional data regarding outcome measures or candidate predictors related to the included RCTs that may not have appeared in any of the trial publications. We have clarified this in the protocol (page 13, line 21-22).

Ethical approval issues have been encountered for a few trials. For a couple of trial teams this meant that they were not able to share data, despite their willingness to contribute. For one trial, the trial team decided to go back to all participants and ask for their additional consent. As explained in our response to comment 4, we will report on these issues, as they are important, once the process of contacting authors, agreeing participation, and sharing data has been completed.

Reviewer #2

Thank you for the opportunity to review this work. This is a protocol of an individual participant meta-analysis that aims to investigate the potential effect modification of shoulder pain treatment based on a number of predefined candidate predictors. Potentially, the results of this study will be important for the clinical practice of shoulder pain management. I am providing few comments that hopefully you will find helpful.
(1) The methodology is clearly described, however there are several inconsistencies between the manuscript and the protocol registered in PROSPERO (eg. The reported search strategies are somewhat different), partly because the PROSPERO protocol is somewhat dated.

Response: We would like to thank the reviewer for this comment, and have now amended the PROSPERO registration to ensure consistency with the protocol.

(2) P10 Searching and selection section: Please, clearly mention the databases that were/will be searched.

Response: Updated searches of electronic databases (restricted to randomised controlled trials) included: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), PEDro, WHO ICTRP and ClinicalTrials.gov (now listed on page 11, lines 9-11).

(3) P16 L12-14: "If studies use different pain or disability scales, these will be converted to a common scale if possible or otherwise estimates will be expressed as standardised mean difference." Regressing on the final scores after adjusting for the baseline values and regressing on the standardised mean difference are two separate analyses which address different questions and it is not guaranteed that they will provide similar results. Instead, using the z-transformed outcome values and adjusting for the z-transformed baseline values may be a better way to address the former question.

Response: We agree. In our analyses, we will always adjust for baseline values when modelling continuous outcomes. Therefore, if the obtained IPD allow us to model the original continuous scales, we will use a final score adjusted for baseline score approach (ANCOVA). However, if standardised scales are required, then we will regress the standardised final score adjusted for the standardised baseline score. We have now added this to the revised manuscript (page 17, lines 16-17).

(4) P16 L17-18: The use of fractional polynomials or splines for assessment of non-linearity. However only fractional polynomials are mentioned in the abstract and in the sensitivity analyses sections. Will splines be used?

Response: Due to recent (unpublished) research conducted since submission, we have found that splines are more appropriate in this context methodologically, as fractional polynomials can lead to different equations per study (making them impossible to pool in a 2-stage approach), and are problematic when the distribution of covariate values is not consistent across studies. This can be better handled with splines and appropriate knot positions. Therefore, we have replaced
fractional polynomials with restricted cubic splines throughout the manuscript, with reference to Gasparrini et al. (reference 65 added):


(5) P17 L14-20: Please note that in an IPD meta-analysis the use of Egger's test and Peter's test will not necessarily correspond to the evaluation of small study effects, but to possible non-participation bias.

Response: These tests are always about detecting small study effects. The cause of this issue could be multi-faceted, including publication bias, heterogeneity, or other reasons such as non-participation bias as you say. But the key issue is to detect small study effects (systematic differences in the results obtained for small studies and larger studies). We have added a comment (page 18, lines 19-21) that small study effects could be due to many reasons, such as publication bias, heterogeneity, and availability bias (i.e. non-participation of trials toward the IPD meta-analysis).

(6) Reviewer #3: The protocol of the IPD meta-analysis is well written and all required aspects have been appropriately covered. I have no additional comments on the manuscript.

Response: Many thanks!