****Please find author responses below in bold text****

25-Jul-2018

Dear Dr. Crocker

Manuscript ID BMJ.2018.045186 entitled "Assessing the impact of patient and public involvement (PPI) on enrolment and retention in clinical trials: a systematic review and meta-analysis"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

Thanks!

Daoxin Yin
dyin@bmj.com

*** PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. ***

https://mc.manuscriptcentral.com/bmj?URL_MASK=3457f3f8e4de4255abbdc6fa085de3a7

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Wim Weber (chair), Richard Riley (statistician), Sophie Cook, Jose Merino, Elizabeth Lower, Georg Roggla, Daoxin Yin, Tiago Villanueva

Decision: Put points after the stats report

Detailed comments from the meeting:

The committee agreed that it is a very important topic. The 7th decision letter is from our statistician (Prof Richard Riley), please pay close attention and follow all the instructions. And editors particularly anticipate the replies to heterogeneity and expect the authors can explain, interpret and discuss the PPI appropriately. Please also make the point-by-point replies to other reviewers' comments.

Authors' response: Thank you for giving us the opportunity to address the reviewers' comments. We have found them very helpful and believe the paper is much improved as a result, so have added the following sentence to the Contributorship statement: 'We also thank the peer reviewers for their constructive comments which helped to improve this paper.' Please see below our point-by-point responses to the comments. We have followed all the instructions given by Prof Riley and hope these are satisfactory.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
I found this study very interesting and I felt it was very well written and explained, even for non-scientists. This was then "explained" by revealing that one of the authors is a patient partner. To me as a patient reviewer this made all the difference to reading and understanding the study. The other aspect I also found very positive and important was the distinction between PPI with no lived experience and PPI with lived experience. I have no comments to the authors, other than that I felt the findings etc were excellently explained.

Authors' response: Thank you for your comments. We are pleased that you found our article interesting and easy to understand.

Additional Questions:
Please enter your name: Kerstin Morrison

Job Title: Teacher

Institution: Primary school

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
A very well written piece of work. As a patient advocate I believe phenomenology "the lived experience" as research is not seen enough. A perspective at the grass root level doesn't always match academic recommendations- in this respect I believe that the appropriate papers were sourced and reviewed, with the relevant studies included. The authors provide data for rationalizing their decision, and provides a digestive "layman's summary" of information. Research such as this can provide quality improvements strategies to healthcare.
The aim to measure I believe succeeded and explores various impact. There is a clear authorship disclosure and I believe a realistic analysis could divulge instruments and mechanisms to better support. The lack of patient lead, patient incorporated research is lacking- lived experience from patient perspective could be key in better supporting

Authors' response: Thank you for your positive comments. We hope that this study will serve to further the endorsement of lived experience in PPI activities.

Additional Questions:
Please enter your name: Julie Sprakel

Job Title: Founder & President

Institution: Think Pink: Bahrain Breast Cancer Society

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here:

Reviewer: 3

Recommendation:

Comments:
First, this study is a well-designed and well-conducted systematic review. The results make a significant contribution to our understanding of the impact of PPI on enrolment in clinical trials. Therefore, the review deserves to be published.

Authors' response: Thank you for your support.

Second, below please find my answers to the patient perspective questions.

Question 1: ARE THE STUDY'S AIMS AND THE ISSUE AND QUESTIONS THAT THE PAPER ADDRESSES RELEVANT AND IMPORTANT TO YOU AS A PATIENT? DO YOU THINK IT WOULD BE RELEVANT TO OTHER PATIENTS LIKE YOU? WHAT ABOUT CARERS?

As a patient and a patient research partner I find patient and public involvement (PPI) in research very important. Equally important is the assessment of any impact such involvement may have.

From a researcher/funder/taxpayer point of view the main focus of such assessments would perhaps typically be on the effectiveness or cost-effectiveness of PPI, whereas for patient research partners the focus may be different. For patients who donate their time to take part in research the most important thing may well be that they feel that they are being treated as equal partners and that their viewpoints are being acknowledged and incorporated somehow. In short, that their participation is meaningful and worthwhile. I would like to see more qualitative studies exploring patient partners' experience and perception of their role as patient research partner.

I find that the aim of the present review – Assessing the impact of PPI on enrolment and retention in clinical trials – to be of more immediate interest to researchers and funders than to patients and patient research partners.

Authors' response:

Thank you for your insight. We agree that patients' experiences of involvement, and how they are treated by researchers, are extremely important parts of assessing the impact of PPI. Although we were unable to address this in the current systematic review, we recently carried out a qualitative study exploring PPI contributors' views and experiences of involvement, including their views on PPI impact and its assessment (Health Experiences Research Group 2014; Crocker *et al.* 2017).

We agree that the outcomes 'enrolment' and 'retention' may be of greater interest to researchers and funders than to patient research partners. Nevertheless, our patient partners were involved in deciding how to assess PPI impact and felt these outcomes were important enough to warrant particular focus.

References:

Health Experiences Research Group. Patient and public involvement in research: University of Oxford; 2014. Available from: http://www.healthtalk.org/peoples-experiences/medical-research/patient-and-public-involvement-research/topics.

Crocker JC, Boylan A-M, Bostock J, Locock L. Is it worth it? Patient and public views on the impact of their involvement in health research and its assessment: a UK-based qualitative interview study. Health Expectations. 2017;20(3):519-28.

Question 2: ARE THERE ANY AREAS THAT YOU FIND RELEVANT AS A PATIENT OR CARER THAT ARE MISSING OR SHOULD BE HIGHLIGHTED?

The authors quote the patient partners involved in this study as arguing that "a trial that recruits more quickly will ultimately benefit patients more quickly". I think that if I had been involved in this study I would have seen it as part of my role to raise some of the following critical questions:

- Could there be any negative implications of patient involvement in enrolment and retention in clinical trials?
- Should we, as patients, naively assume that all trials are conducted for our benefit?
- Should we automatically endorse every trial?
- Do we possess the knowledge and skills to critically assess the risks involved on behalf of our fellow patients?
- Is it ethical for patients to help 'persuade', directly or indirectly, other patients to enrol in trials?

Authors' response: Thank you for raising these important issues. We feel they warrant attention in the limitations section of the paper and have added the following paragraph: 'Finally, the findings of this study say nothing about the quality or ethical acceptability of PPI in the included studies, or indeed patient views on the importance of the clinical trials being conducted. PPI may improve enrolment, but this does not rule out negative impacts such as an emotional cost to involved patients (Health Experiences Research Group, 2014) or patients feeling coerced into enrolling. Should patients assume that all trials are conducted for their benefit, and automatically endorse every trial? Do (and should) involved patients have the necessary skills to assess the risks involved on behalf of their fellow patients? These are important dilemmas which are beyond the scope of this study to address.'

Question 3: FROM YOUR PERSPECTIVE AS A PATIENT, WOULD THE TREATMENT, INTERVENTION STUDIED, OR GUIDANCE GIVEN ACTUALLY WORK IN PRACTICE? IS IT FEASIBLE? WHAT CHALLENGES MIGHT PATIENTS FACE THAT SHOULD BE CONSIDERED?

NA

Question 4: ARE THE OUTCOMES THAT ARE BEING MEASURED IN THE STUDY OR DESCRIBED IN THE PAPER THE SAME AS THE OUTCOMES THAT ARE IMPORTANT TO YOU AS A PATIENT? ARE THERE OTHERS THAT SHOULD HAVE BEEN CONSIDERED?

Not quite, cf. the above comments.

Authors' response: Please see our response to point 1 above.

Question 5: DO YOU HAVE ANY SUGGESTIONS THAT MIGHT HELP AUTHOR(S) STRENGTHEN THEIR PAPER TO MAKE IT MORE USEFUL FOR DOCTORS TO SHARE AND DISCUSS WITH PATIENTS?

The authors could incorporate, in a sentence or two, the dilemmas of patient involvement in enrolment in clinical trials mentioned above.

Authors' response: We have incorporated these dilemmas into a short paragraph in the limitations section (please see our response to your point 2 above).

Question 6: THE LEVEL OF PATIENT INVOLVEMENT IN THE RESEARCH DESCRIBED, AND IF AND HOW IT COULD HAVE BEEN IMPROVED

The patient involvement in the present study is described in some detail as part of the Methods section. Apparently patients were involved at every stage of the research process, from planning the study to writing the article. However, only one patient partner took part in the entire process. It would how been nice to know the reasons for this. Also, instead of just stating that "PPI has been a wholly positive experience for us and there are no negative outcomes to report", it would have been good to report all three patient partners' experience as well.

Authors' response:

We initially involved two patients in the project, but one of them retired from PPI activities part-way through the study due to ill health, hence why only one patient partner took part in the entire process. We invited a third patient to join the group at this point, but in retrospect it would have been better to involve at least 3 patients at the outset. This is a lesson we are taking forward into our current work.

With regard to there being "no negative outcomes to report", we were thinking, rather narrowly, about research-related outcomes. However we appreciate that there may be negative (or positive) effects on the individuals involved, and following your suggestion, we asked our patient partners for feedback on their own experiences to include in this paper. They gave very helpful accounts of their experiences, which we have incorporated into the following new paragraph:

'Working in partnership with patients has been a very positive experience for the researchers in the team and we have not identified any negative impacts on the research. Our current patient partners (AC and RH) report multiple positive aspects of their involvement including being interested in the topic and endorsing its importance, feeling welcomed and respected as part of the project team, and feeling that their contributions are valued and responded to. Negative aspects have included difficulty following the conversation and contributing during teleconference meetings (sometimes necessary because of the long geographical distance between RH and the lead author) and having only a limited understanding of the mathematics of the meta-analysis.'

Additional Questions:
Please enter your name: Mette Toft

Job Title: patient, patient research partner

Institution: none

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: None to declare.

Reviewer: 4

Recommendation:

Comments:
Reviewer: Kristin Liabo, Senior Research Fellow, University of Exeter Medical School
This is an impressive piece of work to disentangle claims that working with patients and carers in research can help with participant recruitment. The study has sound methodology which draws on

standard (but often ignored) systematic review methodology. Considering the current demands for patient and public involvement by most health research funders, the results are very important to researchers, research bureaucrats, and patients who want to work with researchers in a partnership capacity. The results are particularly interesting to anyone affiliated with Clinical Trials Units. Because of the broad evidence-base on which this study draws its conclusions the findings have international relevance. This study is a good contrast to many descriptive accounts of 'PPI'.
Overall, this reads well, although it might be less accessible to someone new to patient and public involvement. The article reflects some of the ambiguity (or lack of clarity) in the field (which for lack of an established name can be called 'patient and public involvement' community).

Authors' response: Thank you for your positive feedback. We have responded to each of your suggestions below, including expanding our description of PPI to make the paper more accessible to readers who may be new to PPI.

My comments below are not on the soundness of methodology, but a suggestion for how you might shift the reporting to be clearer:
First, while I don't agree with you that working with patients as partners equates to an intervention, I am convinced by your article that this works well for the purposes of your systematic review. This works, for me at least, since you have anchored it in trials' need for improved recruitment. My suggestion is therefore that you stick more consistently to this starting point throughout your reporting.
For example, on page 6, you suggest that "the consequentialist argument for PPI in clinical trials … is likely to play an important role in the adoption of meaningful PPI as routine…" Here, you leave the question 'how can we improve recruiting trials?' and focus on improving the argument for PPI through establishing an evidence base. The difference is subtle, but I believe your message would be clearer if it is written with the focus of improving trials, rather than also including arguments for improving or strengthening the case for PPI. I know they link, but I don't think this is purely a semantic issue: the first message is clearer if you leave out the second.

In regards to your title, this message could be reinforced by changing it to something like "How can we improve recruitment rates in clinical trials? Would working with patients on the study planning help?" (I appreciate I am not particularly good at titles!)
If you, and the editors, agree with this point, you would need to change your introduction and anchor it in literature on trial recruitment. Unfortunately I am not familiar with the problems and solutions reported elsewhere to make any suggestions, but I believe this study could fit nicely there rather than as it currently does: in-between methods studies to improve trials and studies that seek to evidence the importance of PPI. This sharpening of your focus would also have implications for your recommendations for future research (p16) where you would anchor this in all other strategies for improving recruitment (as well as your current focus on understanding patient partnership work more).

Authors' response: Thank you for your suggestions. We agree that the framing of PPI as an intervention works in the context of a recognised problem that needs solving - in this case, the need to improve recruitment and retention in clinical trials. However, we do not agree that the focus should be steered away from the PPI impact debate. This study emerged from the funder's desire to assess the impact of PPI, rather than to address the problems of trial recruitment and retention. There is a strong desire in the biomedical research community to quantitatively assess the impact of PPI, and we believe that this study is as important to the PPI impact research agenda (thus far dominated by qualitative studies) as it is to the agenda to find interventions which

improve recruitment and retention in clinical trials. This is why we have given approximately equal space to the two different arguments for carrying out this piece of work. We believe a key strength of the study is its ability to contribute to both areas of research. We also note that reviewer 6, an expert in trial recruitment research, focused on the PPI impact debate in the introduction to his feedback: 'Patient and public involvement is rightly seen as a critical part of the delivery of health services research, but there is a developing debate about its impact, over and above any moral arguments about its importance. One of the oft-made arguments about the benefits of PPI is the potential to make studies more acceptable to patients (both in terms of their aims, and the specifics of how they are run), which may have impacts on recruitment and retention, but the evidence is fairly weak. If PPI was shown to demonstrably improve recruitment and retention through enhancing acceptability, this would be a very high profile finding, of great interest to the research community, and the paper likely highly cited. This review attempts to explore whether PPI has those impacts through a systematic assessment of the available evidence, and is a welcome addition to the literature.'

Second, swapping the acronym PPI with full, descriptive, words might also improve clarity. For example, on page 11 you say that studies 'used PPI'. I believe this would read better if you said 'worked with' or 'involved patients in'. I sometimes find it difficult to understand what the PPI and the non-PPI interventions mean in the context of the sentence and spelling out words is likely to help with this. For example, also on page 11 you say that "Many of the PPI interventions also included non-PPI components… " I find this quite confusing because in my experience, when working with patients, it is often not easy to disentangle which suggestions for recruitment (or any other decision on study design) came from researchers and which came from patients. I appreciate this will add slightly to your word count. I believe it is important to get this right and delete some details or shorten sentences elsewhere.

Authors' response:

Thank you for your suggestion. We have reduced the number of PPI acronyms used in the paper as nouns by replacing them with descriptive words where appropriate. For example: 'studies used PPI' has been replaced with 'studies involved patients or lay people'; 'including PPI in health research' has been replaced with 'involving patients and members of the public in health research'. The exception is when we refer to 'PPI interventions' because we feel that replacing the adjective 'PPI' with descriptive words could actually make it more difficult to read. In addition a very precise understanding of PPI is required in relation to the interventions included in our review. We hope that our detailed, operational definition of PPI in the Methods helps in this regard.

We appreciate that the reference to 'non-PPI components' could be confusing because as you rightly point out, it is often not easy to disentangle the impact of PPI from the impact of researchers or other involved stakeholders. For clarity, we have added to our search methods that 'we included interventions in which PPI was integrated with additional components inseparable from the PPI (such as other stakeholder involvement) because this is consistent with the way patients are often involved in practice (e.g. being part of an advisory group). Hereafter we refer to such components as 'non-PPI components' of interventions.' In addition (and in response to reviewer #7 point 12) we have added to the abstract that 'some PPI interventions included additional components inseparable from the PPI (e.g. other stakeholder involvement)' and that 'it is possible that non-PPI components of interventions may have contributed to this effect'.

Some details which as a typical peer-reviewer I can't help comment on (but which are less important than my two points above):
I would recommend cutting details on previous studies to assess impact from involvement (keeping these references but cutting it down) and details on your very comprehensive and impressive methods to make room for an example or two of what patient and carer involvement might look like. This would help people new to it to envisage what the intervention you are referring to looks like. The INVOLVE definition is helpful, but could be cut to make room for something more descriptive.

Authors' response: Thank you for this helpful suggestion. We have added the following text to the Introduction (immediately after the INVOLVE definition of PPI): 'There are many different types of involvement, from one to many individuals or whole patient organisations, one-off involvement in a particular aspect of the trial (e.g. reviewing draft information for patients or recruiting participants from their communities) to involvement throughout the trial (e.g. as members of a Trial Steering Committee), and involvement with no decision making power (e.g. as advisers) to involvement in decision making as equal partners.' In view of the BMJ's lack of a strict word limit for online publications, we would prefer not to cut out important details of our methods and background information about previous studies assessing PPI impact (please see also our response to your first comment).

As mentioned before I was confused by the non-PPI reference (e.g. page 11 and 15).

Authors' response: As detailed in response to your 2nd point above, we have clarified what we mean by this in both the Methods and Abstract.

On page 12 you refer to the study where involvement was associated with lower enrolment. You do not say what kind of involvement this was, but you do describe the involvement of the most successful trial (Vincent et al). It would be helpful to have the same information in the text on both trials, especially if the studies worked with people in similar ways.

Authors' response: We have reworded our description of this study so that it is more similar to the description of Vincent *et al.*'s study, and hope this is now clearer: 'In this study, lay community members (faith-based organisations) attempted to directly recruit African Americans with diabetes to the trial; however this yielded a lower enrolment rate than recruitment via the health system (non-PPI)…'

I am unclear, on page 14, why you refer to not identifying any studies which assessed the impact of PPI in developing the trial question or designing the trial itself. Do you mean impact from this kind of involvement on recruitment?

Authors' response: Yes and apologies for the lack of clarity. We have reworded this sentence: 'We did not identify any studies which assessed the impact on enrolment or retention of PPI in developing the trial question or designing the trial itself.'

Also on page 14 you say that it is unclear how PPI contributors can benefit research through their role as 'expert in lived experience' – do you mean in what formats they would be involved, or how

they use their lived experience, or in regards to what roles? Perhaps all? I found this a bit vague, but might be because my head is in the particularities of involvement on a daily basis.

Authors' response: Apologies for the lack of clarity. We have reworded the second part of the sentence so that it now reads: '…the precise mechanisms linking such expertise with improvements in enrolment and retention are unclear - something which we are exploring in a complementary realist analysis of the included studies.'

The last paragraph on page 14 is also a bit unclear. When you say "none of the PPI interventions included people with lived experience of the health condition under study… " do you mean the interventions in the studies that evaluated the impact on retention or do you mean all studies? Because the paragraph starts with the retention studies I wondered whether this second sentence related to the first, or if it was making a separate point?

Authors' response: Again, apologies for the lack of clarity. We have reworded the sentence: 'None of the PPI interventions in the retention analysis included people with lived experience of the health condition under study, and most of them primarily targeted enrolment rather than retention.'

Table 1: Intervention: is there some typos in the first sentence? Meaning is clear but the structure is odd. Do you mean "A trial methodology intervention which was consistent with the INVOLVE definition of public involvement"? Late in this same cell it sounds like you included it as PPI if researchers or health professionals had the condition under investigation? This sounds a bit odd to me, but perhaps this is common practice? It illustrates the whole variety of forms that 'PPI' can take but I wonder how people balance that those different hats.

Authors' response: Thank you for your suggestions. We did include as PPI researchers or health professionals who had the condition under investigation, including so-called 'service user researchers' commonly seen in mental health and disability research. We have clarified this in Table 1: 'The PPI contributor(s) had to be either a patient, carer or lay member of the public; research or healthcare professionals with the health condition under investigation were included as PPI, but research or healthcare professionals only sharing a characteristic with the target population *other* than health condition (e.g. ethnicity, gender, age) were excluded.' We have also reworded 'trial methodological intervention' to 'trial methodology intervention'.

I look forward to seeing the published version of this work.

Authors' response: Thank you for reviewing our paper and for your helpful suggestions.

Additional Questions:
Please enter your name: Kristin Liabo

Job Title: Senior Research Fellow

Institution: University of Exeter Medical School

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: As someone employed by a programme grant to specifically support their involvement of patients and carers in research I have a vested interest in sustaining such involvement.

Reviewer: 5

Recommendation:

Comments:
This is a well conducted systematic review of the impact of PPI interventions on recruitment and retention in clinical trails. Although the review examined a wide range of variables, it was not possible to be specific about which aspects of PPI impacted on trial retention. While this is useful and thought provoking data I feel it adds little to what is known explicitly or implicitly on the subject. My recommendation would be that the authors incorporate the findings from their ongoing realist analysis with this review with and publish both together. I feel that this would give a more rounded and informative analysis as, in my opinion, details of the interventions are what readers will be looking for.

Authors' response:

Thank you for your comments. We agree that many people already doing meaningful PPI may feel intuitively that it improves recruitment and retention, or may have witnessed real improvements in recruitment and retention as a result of PPI. They may not be surprised by our findings. However, many trialists and biomedical researchers are still sceptical about the benefits of PPI (see e.g. Health Experiences Research Group 2014), and we believe this group of people may have more to gain from our findings. In addition, it is a first attempt to estimate the size of any benefit of PPI on enrolment and retention.

We appreciate your suggestion to combine the findings of this review with the findings of our ongoing realist analysis, the latter of which will shed more light on the mechanisms of PPI impact.

However, given the different aims (theory development rather than hypothesis testing), philosophical underpinning (realism rather than positivism), timing and sheer size of the project, we believe that it will sit better as a separate, follow-on paper to complement the meta-analyses reported here.

Reference: Health Experiences Research Group. Patient and public involvement in research: University of Oxford; 2014. Available from: http://www.healthtalk.org/peoples-experiences/medical-research/patient-and-public-involvement-research/topics.

Additional Questions:
Please enter your name: Roberta James

Job Title: SIGN Programme Lead

Institution: Healthcare Improvement Scotland

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here:

Reviewer: 6

Recommendation:

Comments:
Thank you for the opportunity to review this interesting paper.

Patient and public involvement is rightly seen as a critical part of the delivery of health services

research, but there is a developing debate about its impact, over and above any moral arguments about its importance

One of the oft-made arguments about the benefits of PPI is the potential to make studies more acceptable to patients (both in terms of their aims, and the specifics of how they are run), which may have impacts on recruitment and retention, but the evidence is fairly weak. If PPI was shown to demonstrably improve recruitment and retention through enhancing acceptability, this would be a very high profile finding, of great interest to the research community, and the paper likely highly cited.

This review attempts to explore whether PPI has those impacts through a systematic assessment of the available evidence, and is a welcome addition to the literature.
The methods of the review are generally strong, with a good range of databases searched, and a decent number of studies included in the analysis. The process of the review is conventional and I could identify no major issues in terms of the mechanics of the review.

Authors' response: Thank you for reviewing our paper and for your positive comments.

I had two concerns. The first related to the definition adopted, and the implications for the range of studies included. The second concerned the types of studies included, and the data analysed.

Authors' response: Thank you for highlighting these concerns. We have responded to each one below.

The introduction includes a very broad definition of PPI, but I am not sure that is sufficient for the review, and greater detail could usefully be provided on the range of interventions included in the study. Table 3 does provide some detail, but it is quite limited. My understanding is that their 'take' on the scope of PPI is quite broad. For example, the Du et al (2008) study is of a video intervention, and reading the detail does not suggest it is PPI as conventionally understood in the UK (although I can understand the logic of its inclusion). Likewise, Dear (2012) is a test of a 'consumer-friendly website', while Man (2015) is a trial of user testing (one in which I was involved, and which we did not conceptualise as PPI, although it is reasonable that others do).

Again, I think these inclusions are justified, but I am not sure my initial reading of their paper really made it clear the range of interventions being considered here. The highlight findings of this paper will be potentially very high profile, and it is really important that readers (especially readers of the abstract) are aware of what is being tested here. There is a slight danger that readers will make assumptions about 'PPI' in the title. The authors could be encouraged to highlight the fuzzy boundaries here a little more clearly, and highlight how their definition relates to conventional understanding of the term 'PPI'.

Authors' response: Thank you and we agree that this is important to clarify. We have added the following sentence to the abstract: We define 'PPI' as any form of active patient, carer or lay involvement, including e.g. membership of a trial advisory group, user testing and peer recruitment.'

We have also added to the Methods section: 'We defined 'PPI intervention' as a trial methodology intervention which was, or included as an active component, any form of PPI consistent with the INVOLVE definition of public involvement: 'research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them', where the term public includes patients, potential patients, carers and people who use health and social care services as well as people from organisations that represent people who use services.(10) This included interventions not necessarily labelled or conceptualised as 'PPI' by the study authors e.g. user testing, peer recruitment and community-based participatory research.'

I think the extension of the study beyond trials is justified, but I was a little unclear as to what these studies looked like. For example, the example given is a study looking at the effect of PPI in the early stages of trial design. What did such a study look like, as it was not entirely clear what the comparator was in such a design? This might be usefully clarified with some examples, as this is clearly a slightly unconventional literature.

Authors' response: **We have added the following text to the Methods section: 'We accepted all non-randomised study designs (provided there was a direct comparison group), including non-randomised controlled trials, controlled and uncontrolled before-after studies, and observational studies. Comparison groups were patients unexposed to the PPI intervention (e.g. before its introduction) or patients exposed to an alternative intervention with no PPI (e.g. recruitment via healthcare professionals).' We hope this clarifies what types of non-randomised studies were included.**

In the same way, more detail on the data extracted from the non-randomised studies would be useful. Again, I am interested in exactly what data were extracted from non-trials, and more details and examples might help here. For example, I was unsure how the data for Iliffe (2003) for the meta-analysis were derived from the paper, as it was not clear to me how they went from the figures in the paper to the quoted odds ratio. Initially I had the same issue for Wisdom (2002) as I was not clear where the 1177 sample was derived, although digging into the detail of the paper eventually made it clearer.

Authors' response:

Iliffe 2003 was one of the observational studies (along with Tenorio 2014 and Tenorio 2011) for which we had to use a proxy denominator in the absence of absolute numbers of exposed patients (as already mentioned in Table 2 description of outcomes data). We compared the proportion of total participants recruited from intervention-exposed regions before vs. after the PPI intervention, and have now clarified this in Table 3c column 3. Your comment made us reflect more deeply on the limitations of these data, and as a result we have added a sensitivity analysis which excludes studies using a proxy enrolment rate denominator from our secondary analysis (see Methods). We found that this not alter the findings (see Results section). It does not apply to our main analysis because the randomised studies all reported the absolute numbers required for analysis.

We have also clarified which denominator we used from the Wisdom 2002 study in Table 3c column 3. And we have added a new column to this table entitled 'Total number of participants',

so that readers do not have to refer only to the forest plots for this information.

I think it would be really helpful to actually include the recruitment data analysed (i.e. numerator and denominator in each 'arm') in the Figure, rather than just the overall sample size. This would help people understand what was being analysed, and how it related to the data in each paper. It would also be useful to clarify whether all the comparisons were contemporaneous, or whether some related to rates being compared across different time periods of the trial.

Authors' response: Thank you for your suggestion. We have added the precise numerators and denominators used in PPI and comparator groups to our main enrolment and retention forest plots (Figures 2 & 3 and Appendices 4 & 5). As mentioned above, we have also made explicit that before-after study designs were included, thus clarifying that comparisons did not have to be contemporaneous. Table 3c (final column) already states the design of each included study.

The abstract suggests that the effects of PPI are not influenced by study quality, largely on the basis that the results are significant irrespective of the inclusion or exclusion of high risk of bias. However, the magnitude of the effect is quite different, and this might be made clearer. It also might be helpful to give an idea of what sort of effect that might be demonstrated in a conventional trial, making some reasonable assumptions about baseline response rates. The effect that they have demonstrated is important, but quite modest, and it is important that people are aware that this is just one way of making improvements to trial recruitment. Being more explicit about what those effects might look like for a trial would be useful

Authors' response: In response to reviewer #7's recommendations, we have made the randomised- only analysis our main analysis rather than a sensitivity analysis. Now, when the one study at high risk of bias is removed, there is almost no change in effect size. We agree with you that the effect size is modest, and have added this term to the abstract, lay summary and results section ('on average, PPI interventions modestly but significantly increased the odds of participant enrolment'). In the Discussion section, we have also translated the 95% prediction interval into real terms, which we hope gives an idea of the effect one might expect in a typical trial: 'To illustrate what our main findings could mean in practice: in a hypothetical sample of 1,000 patients, where typically 100 enrol (consistent with the 10% average enrolment rate in our sample of randomised studies), a PPI intervention similar to those included in our main meta-analysis would likely lead to between 1 and 30 (average 14) extra patients being enrolled.' We have also added this information to the 'What this study adds' section.

The authors might also be encouraged to be more specific as to the types of PPI that need further evaluation, which may relate to their comment on mechanisms.

Authors' response: We have added to the 'future research' section and abstract that we need to assess 'which types of PPI work best in different contexts'. Our realist analysis is looking at all types of PPI in the sample to try to address this gap in understanding. We have also already highlighted in both the 'future research' section and abstract that PPI in early trial design and PPI specifically targeting retention need particular attention because of the lack of evaluations of these types of PPI in relation to enrolment and retention outcomes.

I was not sure why the result around lived experience was 'unsurprising'? I felt that this paragraph was a little unclear and would benefit from rewriting.

Authors' response: We realise that this result may not be unsurprising to all readers, and have removed this subjective viewpoint. We have also reworded the whole sentence to improve clarity (also in response to reviewer #4's comment). It now reads: 'This is consistent with the view that PPI contributors can benefit research through their role as 'expert in lived experience',(61) though the precise mechanisms linking such expertise with improvements in enrolment and retention are unclear - something which we are exploring in a complementary realist analysis of the included studies.'

Additional Questions:
Please enter your name: Peter Bower

Job Title: Professor of Health Services Research

Institution: University of Manchester

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: I was the PhD supervisor of one of the authors, and we have 1 current shared grant

One of my trials was included in the review

Reviewer: 7

Recommendation:

Comments:
This is a very interesting study. To me, it is an excellent example of a situation where there is expected to be heterogeneity (due to the broad range of interventions and disease areas), but still a summary of the evidence is important to gauge the average impact of PPI and, indeed, the range of PPI impact across different settings. I think the authors have done well to convey this, in particular by emphasising that their pooled results represent average affects, and by reporting prediction intervals to disseminate the range (heterogeneity) more clearly. It raises debate and discussion for new research. There are some strong limitations, but I think it adds an important starting point for further work. I have reviewed this from a statistical perspective, and do have some recommendations and comments for improvement:

Authors' response: Thank you for your positive comments and recommended improvements. We have responded to each one below.

1) The inclusion of non-randomised studies was confusing to me. Indeed, the findings only seem to be strong when excluding these studies in the end. As there is already potential heterogeneity across different types of PPI in the trials setting alone, I find the extra heterogeneity from mixing trials and observational studies to be hard to justify, at least at the main analysis. I would prefer, therefore, that the main (primary) analyses are those restricted to just the trial evidence.

Authors' response:

Thank you for your suggestion. We originally included non-randomised as well as randomised studies in order to avoid excluding many types of PPI intervention which would not be amenable to randomisation (e.g. PPI in the early stages of trial design). However, we agree that given the heterogeneity across different types of PPI and trials settings, introducing extra heterogeneity from mixing study types could be problematic. We have therefore re-organised our analyses so that the main analysis includes only randomised studies (Figure 2), with a secondary analysis including both randomised and non-randomised studies (Figure 3). Because this differs from our original protocol and PROSPERO database entry, we have explained it in the Methods section as follows: 'Because of high methodological and statistical heterogeneity across non-randomised studies, we made a post-hoc decision to present findings from randomised studies only as our main analysis. We then conducted a secondary analysis including non-randomised as well as randomised studies.' In Figure 1 (PRISMA flow diagram), we have added two boxes to show the number of randomised studies included in the main enrolment and retention meta-analyses. In Table 4 (aggregate characteristics of included studies), we have moved the row labelled 'Study design' (randomised / non-randomised) up to 3rd row to reflect its relative importance. In the main text, we have moved the risk of bias assessment results for randomised studies so that they are now reported *before* the corresponding results for non-randomised studies.

We have retained non-randomised studies in the exploratory subgroup analyses because we believe that inclusion of the full diversity of PPI interventions is important for these exploratory analyses (some of which include exploring the effect of different types of PPI). The reduction in sample size from excluding non-randomised studies would also make many of the subgroup analyses impossible or inappropriate.

We have performed the pre-specified sensitivity analyses on both the main analysis (randomised studies only) and the secondary analysis (randomised and non-randomised studies combined).

2) "We did not find evidence that PPI interventions improve retention in clinical trials (OR 1.20; 95%

CI 0.68 – 2.12)." – needs to be re-worded as clearly confidence interval is wide; indeed, there is also no clear evidence that PPI interventions do not improve retention in trials. Same comments applies to: "Pooling the data in a meta-analysis found that, on average, PPI interventions were not significantly associated with retention of study participants". I'm sure the authors agree that lack of statistical significance is not evidence of no effect, and actually here may merely reflect low power. We cannot rule out potentially large effects (in either direction). So suggest a more balanced interpretation.

Authors' response: We have reworded the various sentences regarding our retention findings as follows:

Abstract: 'The findings with regard to retention were inconclusive due to the paucity of eligible studies (OR 1.20; 95% CI 0.68 – 2.12 for main analysis).'

Lay summary: 'We are uncertain about the effects of PPI on retention because too few studies looked at this.'

Results: 'Pooling the data from 3 randomised studies (4 PPI interventions) in our main meta-analysis did not find a statistically significant effect of PPI on participant retention (OR 1.16 [95% CI 0.33 – 4.14]; p=727).' […] 'Our secondary meta-analysis, combining 5 randomised and non-randomised studies, also found no statistically significant effect of PPI interventions on participant retention, compared with no PPI or non-PPI interventions (OR 1.20 [95% CI 0.52 – 2.77]; p=0.590).'

Discussion: 'Far fewer studies evaluated the impact of PPI interventions on retention of trial participants. They showed, on average, a modest but non-significant improvement in retention; the very wide 95% confidence intervals mean we cannot rule out a potentially large increase or decrease in retention associated with PPI.'

3) "This finding remained after excluding studies at high risk of bias (including all non-randomised studies) (OR 1.17; 95% CI 1.04 – 1.32; 95% prediction interval 1.01 - 1.36)." – there is a big drop in the OR when only considering the high quality evidence; another reason for my suggestion to focus on the trials only evidence as the main analysis. It is reassuring to see that the prediction interval for the OR in a new trial setting contains values > 1, and so – even when accounting for the uncertainty and heterogeneity – it appears likely that PPI involvement is effective.
But is the effect large? That is, can the authors translate to real terms what an OR of 1.17 would actually mean?

Authors' response: We have restricted our main analysis to randomised trials only (please see response to your point 1). In the 'What this study adds' and Discussion sections, we have translated the findings of the main analysis into real terms, which we hope gives an idea of the effect one might expect in a typical trial: 'To illustrate what this could mean in practice: in a hypothetical sample of 1,000 patients, where typically 100 enrol (consistent with the 10% average enrolment rate in our sample of randomised studies), a PPI intervention similar to those included in our main meta-analysis would likely lead to between 1 and 30 (average 14) extra patients being enrolled.' We have also qualified the effect size as 'modest' in the abstract, 'what this study adds' and results section: 'on average, PPI interventions modestly but significantly increased the odds of participant enrolment.'

4) Prediction intervals are calculated how? In a frequentisits setting they are only approximate; in some situations they do not perform well in terms of coverage. It is worth emphasising this.1

Authors' response: We have added to the methods section that 'approximate' prediction intervals were calculated 'using methods reported by Higgins *et al.* (2009)'. We have also added to the limitations section that our 95% prediction intervals should be interpreted with caution because prediction intervals have been reported to be less reliable in meta-analyses with unbalanced study sizes (with reference to Partlett & Riley 2017).

5) Egger's test in inappropriate for odds ratios. Better to use Peters' test, for example.2 3

Authors' response: Thank you for alerting us to this. We have changed this to Peters' test in the Methods (with reference to Peters *et al.* 2006 and Sterne *et al.* 2011). The results of the test indicate no evidence of bias due to small study effects in the enrolment meta-analyses (p=0.924 for main analysis; p=0.592 for secondary analysis) nor in the retention meta-analyses (p=0.435 for main analysis; p=0.412 for secondary analysis); this has been revised in the Results section. We have also removed the reference to Egger's test / publication bias in the Abstract, Lay Summary and Discussion.

6) "Heterogeneity was quantified using the I-squared statistic" – the I2 statistic does not quantify heterogeneity directly; indeed it is a misleading measure in that regard.4 Better measures are the estimate of heterogeneity (or indeed the prediction interval).

Authors' response: Thank you for the interesting and useful reference. We note that an advantage of the I-squared statistic is that it easily interpreted by clinicians as the percentage of variability in the treatment estimates which is attributable to heterogeneity between studies rather than to sampling error. However, it increases with the number of patients included in the studies in a meta-analysis, and so should not be used to decide whether or not to pool treatment estimates in a meta-analysis. We have reworded the relevant sentence so that it now reads: 'We examined heterogeneity using the I-squared statistic, and by calculating approximate 95% prediction intervals…'

7) Confidence intervals from the meta-analysis should be re-calculated to acknowledge the uncertainty in the heterogeneity estimates, for example using the Hartung-Knapp method.5 6

Authors' response: We have recalculated all confidence intervals and added the following detail to the Methods section: 'We used the Hartung-Knapp-Sidik-Jonkman variance correction to calculate 95% confidence intervals reflecting the uncertainty in heterogeneity estimates' (with references to Cornell *et al.* 2014, Rover *et al.* 2015 and Hartung & Knapp 2001). Our findings with regard to statistical significance are unchanged except for the 'pure PPI' sensitivity analysis of randomised and non-randomised studies combined (please see 2nd paragraph of response to point 12 below).

8) What type of PPI intervention is best? Can't say. What is the magnitude of enrolment improvement expected when using PPI? This relates to end of my point 3 – the findings are clearly limited, which is fine, but this needs to be outlined more clearly in the abstract and what this study adds. Recommendations for further research should be about identifying what type of PPI intervention is best for particular settings and contexts.

Authors' response: We appreciate that this study cannot tell readers which type of PPI intervention is best, other than those which include patients with lived experience of the medical condition under study. In the abstract, lay summary, 'what this study adds' and 'Unanswered questions for future research' section of the Discussion, we have added that we need to

understand which PPI interventions work best in particular settings and contexts. In the 'what this study adds' section, we have translated the main findings into real terms (see response to point 3 above), and qualified the effect size as 'modest' in the abstract.

9) funnel plot assessments are better referred to as examination of smalls study effects, rather than publication bias (the latter is just one possible cause)

Authors' response: We have changed the wording in the Methods section ('Peters' test was carried out for each of the two meta-analyses to examine small study effects') and Results section ('Peters' test showed no evidence of bias due to small study effects…').

10) In the what this study adds, it would also help to emphasise that the type of PPI strategy varies considerably across studies

Authors' response: We have added to the first bullet point so that it now reads: 'The nature of PPI, and the impact of PPI on trial enrolment and retention, vary widely between studies.'

11) All meta-regression and subgroup analyses should be reported with caution due to potential for study-level confounding.

Authors' response: Where we refer to the exploratory finding regarding lived experience in the Discussion section, we have added that 'this finding, along with all other subgroup analysis and meta-regression findings, should be interpreted with caution due to the potential for study-level confounding.' In 'What this study adds' we have reworded the reference to our subgroup analysis finding so that it is presented more cautiously: 'Our findings suggest that improvements in enrolment may be more likely when involving patients or carers with lived experience of the health condition under study.'

12) "Many of the PPI interventions also included non-PPI components, such as the involvement of other stakeholders or experts" – so how can we distinguish between the effect of PPI and the effect of experts? Which is the one leading to improvement? Would this lead to a higher risk of bias assessment? Why not start by restricting to those that actually had a pure PPI component to the intervention? Should this also be added to the limitations in the abstract and what this study adds?

Authors' response:

Unfortunately it is not possible to distinguish between the effect of PPI and the effect of other stakeholders or experts in these cases, nor is this captured by the risk of bias assessment tool we used for randomised studies. However, we included these interventions in the main analysis because they are consistent with the way PPI is often done in practice (e.g. patients being part of an advisory group). Further, if we restricted the main analysis (now only randomised studies) to those with pure PPI interventions, only one study would be included (Guarino *et al.* 2006) and meta-analysis would not be possible. We would therefore prefer to prioritise restricting the main analysis to randomised studies only, with pure PPI interventions as a sensitivity analysis. However, we agree that this is an important limitation. We have therefore added to the abstract that 'some PPI interventions included additional components inseparable from the PPI (e.g. other stakeholder involvement)' and that 'it is possible that non-PPI components of interventions may have

contributed to this effect'. To 'what this study adds' we have added that we need to understand 'the specific effects of PPI in partnership interventions (where the impact of PPI is difficult to separate from the impact of other partners – a limitation of the current review).' In the limitations section, we have revised the existing paragraph so that it now reads: 'Many of the PPI interventions included non-PPI components and it was impossible to separate out the effects of these from the effects of the PPI components. When interventions including non-PPI components were excluded in a sensitivity analysis of both randomised and non-randomised studies combined, PPI was still associated with improved enrolment, but with reduced certainty due to the decrease in sample size.'

Please note that due to the Hartung-Knapp re-calculations of 95% CIs, the results of our 'pure PPI' sensitivity analysis of randomised and non-randomised studies combined no longer attained statistical significance. We have therefore changed the relevant Results text to the following: 'The positive overall association between PPI interventions and enrolment remained statistically significant throughout all sensitivity analyses except when excluding interventions with non-PPI components from the secondary analysis (see Appendix 3). Although the estimated effect of PPI actually increased in this analysis (OR=2.70), the exclusion of 15/21 studies yielded a very wide 95% confidence interval (0.83 – 8.84). It was not possible to restrict this particular sensitivity analysis to randomised studies because there was only one 'pure' PPI intervention in this subsample.(Guarino *et al.* 2006)'

13) Six studies could not be included due to insufficient data. Did the authors try to indirectly obtain this data from other information, or even contact the original authors?

Authors' response: In all cases, we contacted authors to provide further information when there were insufficient data reported in available papers (this is already stated in the Methods section). We have added to the Results section that those six studies could not be included 'despite attempts to contact study authors and identify related papers'.

14) "…produced a 95% prediction interval of 1.01 to 1.36, suggesting that any new, high quality randomised study of a PPI intervention would almost certainly demonstrate a positive impact of PPI on enrolment." – careful with this interpretation. The prediction is for a PPI strategy and setting as observed within the included trials, and thus cannot be generalised beyond this as inferred by the authors' statement. Indeed, more is needed about the exact PPI interventions used in the trials that leads to this prediction interval. Did they include non PPI components for example? I think, as per earlier comment, having a section dedicated solely to the trials would aid the clarity and translation of this piece of work, before then broadening out to observational studies also.

Authors' response:

We have removed this interpretation and have replaced it with the following text in the Discussion section: 'To illustrate what our findings could mean in practice: in a sample of 1,000 patients, where typically 100 enrol (consistent with the 10% average enrolment rate in our sample of randomised studies), a PPI intervention similar to those included in our main meta-analysis would likely lead to between 1 and 30 (average 14) extra patients being enrolled.'

We have also changed our main analysis to randomised trials only (as per our response to point 1) and have described the PPI interventions included in this analysis as follows: 'Seven randomised studies (8 PPI interventions) were included in our main meta-analysis. These interventions all

consisted of patient or lay involvement in the design or delivery of patient information, with Ford *et al.*'s intervention also including recruitment sessions hosted by churches in the target community.' In light of this, we have added a further comment to the Discussion: 'As these PPI interventions were mostly restricted to patient or lay involvement in the design or delivery of patient information, the effect size might be even larger for PPI which begins at earlier stages of trial design, since the opportunity to influence patient views and experiences would extend beyond just the provision of information.'

Finally, we have clarified that non-PPI components were included in the main meta-analysis – please see our response to point 12 above.

15) "PPI in developing patient information sheets was not significantly associated with retention,(36, 39) while using lay Community Health Advisers to support participants (the only PPI intervention specifically targeting retention) led to a significant improvement in retention rates (OR 2.52 [95% CI 1.82 – 3.50])."
- but was there strong evidence of a difference between these subgroups based on meta-regression?

Authors' response: We did not carry out subgroup analyses on the retention dataset, and realise now that this statement is misleading. We have therefore reworded it to avoid comparing interventions: **'At the individual study level, only one PPI intervention was significantly associated with retention: this constituted using lay Community Health Advisers to support participants (the only PPI intervention specifically targeting retention), leading to a significant improvement in retention rates (OR 2.52 [95% CI 1.82 – 3.50]).'(53)**

16) Are there small study effects in the trial-only analysis? It does not appear so. This is important to clarify.

Authors' response: Peters' test for the main analyses (randomised trials only) showed no evidence of bias due to small study effects (p=0.924 for enrolment outcome and p=0.435 for retention outcome). We have now included these findings in our Results section.

I sincerely hope this review helps the authors and the BMJ going forward.

Authors' response: Thank you, your review has been very helpful and we hope you are satisfied with our responses. If not, we would welcome further guidance.

Best wishes, Richard Riley

Reference List

1. Partlett C, Riley RD. Random effects meta-analysis: Coverage performance of 95% confidence and prediction intervals following REML estimation. Stat Med 2016.
2. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;342:d4002.
3. Peters JL, Sutton AJ, Jones DR, et al. Comparison of two methods to detect publication bias in meta-analysis. Jama 2006;295(6):676-80.
4. Rucker G, Schwarzer G, Carpenter JR, et al. Undue reliance on I(2) in assessing heterogeneity may

mislead. BMC Med Res Methodol 2008;8:79.
5. Cornell JE, Mulrow CD, Localio R, et al. Random-effects meta-analysis of inconsistent effects: a time for change. Ann Intern Med 2014;160(4):267-70.
6. Hartung J, Knapp G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. Stat Med 2001;20(24):3875-89.

Additional Questions:
Please enter your name: Richard Riley

Job Title: Professor of Biostatistics

Institution: Keele University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: