

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies
<b>AUTHORS</b>	Avery, Kerry; Williamson, Paula; Gamble, Carrol; O'Connell Francischetto, Elaine; Metcalfe, Chris; Davidson, Peter; Williams, HC; Blazeby, Jane

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Maria Bryant and Nimarta Dharni Leeds Institute of Clinical Trials Research, University of Leeds, UK
<b>REVIEW RETURNED</b>	15-Aug-2016

<b>GENERAL COMMENTS</b>	<p>This is a well-articulated, much needed study which has the potential to greatly benefit the scientific community regarding progression criteria from pilot to full RCTs.</p> <p>Major comments</p> <p>The paper is driven by a structural literature review and workshop with experts but it is not clear how each of these contributed to the findings in the paper. There is very little information regarding the search strategy for the review (e.g. what 10 journals, key words etc), which eligibility criteria were used and how the information was synthesised. Were the results of the review presented to the workshop panel? If yes, how? How were discussions structured and recorded? Was there overall agreement? If not, how was this reached? How were discussions synthesised? This information can be easily addressed with a clearly defined methodology section. Text within the results section should then be linked back to the methodology (including information on how many papers were identified); highlighting which findings relate to which method as appropriate.</p> <p>The 10 top tips for success are very useful. They begin with a recommendation to consider red, amber and green instead of stop/go criteria. It would be useful for authors to discuss the merits of this approach earlier on in the paper. A discussion of 'Amber' in particular would be of benefit, including what it might constitute and the sorts of actions that can take place to get researchers back to 'Green'.</p> <p>The paper discusses progression criteria to both stop trials or to improve full trial designs interchangeably. This is important as they ultimately lead to very different outcomes. For example, the abstract says that progression criteria provide an opportunity to optimise the main trial design but many examples provided relate to stopping rules. It would be useful if authors could describe the objectives of progression criteria taking both of these into account in the</p>
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	<p>introduction.</p> <p>Minor comments Much of the text seems to be relevant to external pilot trials in addition to internal pilot trials. This is particularly the case for progression criteria for making improvements to future main trials. It would be useful for authors to mention the application of progression criteria for external pilot trials in the discussion.</p> <p>The opening sentence of the Introduction is a little confusing and would benefit from re-writing.</p> <p>Line 34 – page 5 – The opening sentence of the 2nd paragraph is not needed, as it repeats the end of the 1st paragraph.</p> <p>Line 10 – page 6 – Should setting criteria in advance been deemed 'essential' rather than 'desirable'?</p>
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<b>REVIEWER</b>	Rod Taylor University of Exeter, UK
<b>REVIEW RETURNED</b>	18-Sep-2016

<b>GENERAL COMMENTS</b>	This is an important and original contribution on undertaking internal pilot studies that provide useful guidance to researchers. It well constructed and well reported. This will be an important and highly cited publication in the field. I believe the paper is ready for publication as it is an there is no need for revision. Thank you for the opportunity to review this paper
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## VERSION 1 – AUTHOR RESPONSE

### Reviewer 1

1. The paper is driven by a structural literature review and workshop with experts but it is not clear how each of these contributed to the findings in the paper. There is very little information regarding the search strategy for the review (e.g. what 10 journals, key words etc), which eligibility criteria were used and how the information was synthesised. Were the results of the review presented to the workshop panel? If yes, how? How were discussions structured and recorded? Was there overall agreement? If not, how was this reached? How were discussions synthesised? This information can be easily addressed with a clearly defined methodology section. Text within the results section should then be linked back to the methodology (including information on how many papers were identified); highlighting which findings relate to which method as appropriate.

Revision: Thank you for this helpful comment. The structured literature review that informed this work was previously published in abstract form, which was referenced in the manuscript (page 5, paragraph 3, line 3). In the interests of being concise, we did not think it necessary to present information in the manuscript that had been published previously elsewhere. We have, however, now revised the manuscript to include a section on 'workshop methodology' incorporating additional details of the review (e.g. search strategy, eligibility criteria), the workshop (agenda and production of a workshop summary report) and production of a detailed report on which all workshop attendees were invited to comment. Revisions are highlighted in the manuscript in the following locations: page 5, paragraph 3; page 6, paragraphs 1 and 2.

2. The 10 top tips for success are very useful. They begin with a recommendation to consider red, amber and green instead of stop/go criteria. It would be useful for authors to discuss the merits of this approach earlier on in the paper. A discussion of 'Amber' in particular would be of benefit, including what it might constitute and the sorts of actions that can take place to get researchers back to 'Green'.

Revision: We agree with the reviewer that a more detailed explanation of the stop/amend/go traffic light system for progression criteria earlier in the paper may be beneficial. We have now included an explanation of this concept in the Introduction on pages 4 (last paragraph) to 5 (first paragraph). We have also made a number of revisions to the main body of the text to offer further explanation (page 16, last sentence; page 19, last sentence).

3. The paper discusses progression criteria to both stop trials or to improve full trial designs interchangeably. This is important as they ultimately lead to very different outcomes. For example, the abstract says that progression criteria provide an opportunity to optimise the main trial design but many examples provided relate to stopping rules. It would be useful if authors could describe the objectives of progression criteria taking both of these into account in the introduction.

Revision: We agree with the reviewer that it would be helpful to make clearer the distinction between progression criteria stopping or improving a main trial. We have therefore made a number of changes to the manuscript as follows: Abstract, page 2, paragraph 1; Introduction, page 4, paragraph 2, line 4. 4. Much of the text seems to be relevant to external pilot trials in addition to internal pilot trials. This is particularly the case for progression criteria for making improvements to future main trials. It would be useful for authors to mention the application of progression criteria for external pilot trials in the discussion.

Revision: We agree with the reviewer that many of the points made in this paper regarding the potential value of developing and reviewing progression criteria may also be relevant to how external pilot studies may be used to inform future main trials. We have revised the manuscript accordingly in the Discussion (page 25, paragraph 2).

5. The opening sentence of the Introduction is a little confusing and would benefit from re-writing.

Revision: Thank you for drawing our attention to this. We have rewritten the sentence to improve comprehension (page 3, paragraph 2, first sentence).

6. Line 34 – page 5 – The opening sentence of the 2nd paragraph is not needed, as it repeats the end of the 1st paragraph.

Revision: Thank you for pointing this out. We have revised the manuscript to remove this unnecessary duplication (page 4, paragraph 1, lines 14-16).

7. Line 10 – page 6 – Should setting criteria in advance been deemed 'essential' rather than 'desirable'?

Revision: We have revised the text to read 'may be considered essential' (page 5, paragraph 2).

Reviewer 2

No revisions requested.

We hope that you now consider the manuscript suitable for publication, and look forward to hearing from you.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Maria Bryant University of Leeds, UK
<b>REVIEW RETURNED</b>	28-Nov-2016

<b>GENERAL COMMENTS</b>	The authors have made substantial revisions and I am overall very happy for this paper to be accepted. It is an important paper in its field and has a strong chance of impact. My only minor concern is that there still lacks a bit of methodology related to the review. A structured review is fairly uncommon, and perhaps there should be a note of what this entails in the methods. Authors have suggested that papers were retrieved, but have not included any suggestion regarding what criteria were used. It is possible that all papers were
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	included, but this needs to be stated. In the results, it would be useful to know how many papers were used to inform the workshop discussion. Eight are provided as examples in Table 1, but there appears to be many more in the text citations. Lastly, I would like to commend the group on doing an excellent piece of work -I particularly like the 10 top tips.
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## VERSION 2 – AUTHOR RESPONSE

### Reviewer 1

1. The authors have made substantial revisions and I am overall very happy for this paper to be accepted. It is an important paper in its field and has a strong chance of impact. My only minor concern is that there still lacks a bit of methodology related to the review. A structured review is fairly uncommon, and perhaps there should be a note of what this entails in the methods. Authors have suggested that papers were retrieved, but have not included any suggestion regarding what criteria were used. It is possible that all papers were included, but this needs to be stated. In the results, it would be useful to know how many papers were used to inform the workshop discussion. Eight are provided as examples in Table 1, but there appears to be many more in the text citations. Lastly, I would like to commend the group on doing an excellent piece of work -I particularly like the 10 top tips.

Revision: We thank the reviewer for their helpful comments. We have included further detail explaining the rationale for conducting a structured literature review to inform the current study (page 5, paragraph 3). We have also included additional information about the review methodology, including the inclusion/exclusion criteria used in the review and the numbers of papers identified (page 5, paragraph 3 through to page 6, paragraph 2).

We hope that you now consider the manuscript suitable for publication, and look forward to hearing from you.