

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme
<b>AUTHORS</b>	Walters, Stephen; Henriques-Cadby, Ines; Bortolami, Oscar; Flight, Laura; Hind, Daniel; Jacques, Richard; Knox, Christopher; Nadin, Ben; Rothwell, Joanne; Surtees, Michael; Julious, Steven

### VERSION 1 - REVIEW

<b>REVIEWER</b>	David Torgerson York Trials Unit Dept of Health Sciences University of York YORK
<b>REVIEW RETURNED</b>	30-Nov-2016

<b>GENERAL COMMENTS</b>	Paper is a descriptive study of the recruitment rates from HTA trials. It is interesting to those of us who do HTA trials and it is well written and I have no suggestions to make.
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<b>REVIEWER</b>	Robin Prescott Emeritus Professor of Health Technology Assessment, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh UK
<b>REVIEW RETURNED</b>	13-Dec-2016

<b>GENERAL COMMENTS</b>	<p>I congratulate Professor Walters and colleagues on an eminently readable and informative paper. There are just a few comments that I would like to make.</p> <p>Any review of clinical trials that is based on those that have had their results published is inevitably in danger of reporting a biased sample of the trials that have been started. Others may fail for various reasons including poor recruitment. In this review of trials that have been published in the NIHR HTA journal from January 2004 to April 2016, the risk of this kind of bias may be appreciably diminished. My own experience of the monitoring of projects funded by the NIHR HTA programme leads me to expect that such failures will have been rare, if they have occurred at all. However, not all readers, particularly those outside the United Kingdom, will have this privileged insight. I wonder if the authors can take their review a little further and can quantify the extent to which the review of published trials reflects the population of trials that have been funded by the NIHR HTA Programme? The grants from this Programme are surely</p>
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	<p>a matter of public record, capable of being checked against the trials identified by this survey. Even more simply, I would expect cooperation from the NIHR in supplying the required information, possibly in an anonymised form if necessary, in view of their common interest in the topic of this paper. If the authors cannot fill this gap, I think it is a topic that can usefully be considered within the Discussion. If the gap can be filled, a review of trials funded by the United Kingdom Health Technology Assessment Programme (as indicated in the title of the paper) will be more valuable than the actual review of just those trials whose results have been published.</p> <p>I note that this review has excluded cluster randomised trials for sound reasons that are explained within the Inclusion/Exclusion criteria. Figure 1 has a box that explains that 612 reports were excluded as “not a report of an RCT nor a report of a cluster RCT”. This implies that there were no cluster randomised trials within the 778 title and abstracts screened. I find that sufficiently surprising that I think it is worth mentioning directly in the first paragraph of Results. That will avoid any suspicion that the wording of the box could be inexact.</p> <p>Another exclusion is the 11 pilot studies. While this is sensible if a pilot study was always the objective, I am aware of situations where a definitive trial has been changed to a pilot study as a result of poor recruitment. No doubt the authors have checked that this is not the case, but explicit mention of this in the paper would remove any doubt.</p> <p>Within the tables, ‘other’ is sometimes used as a category without further specification. Some of the ‘other’ categories are quite numerous and I find it slightly disconcerting that there are no footnotes to provide further detail.</p> <p>The authors have been careful to describe their study as a review and not a systematic review and, indeed, have not strictly followed the PRISMA guidelines for reporting systematic reviews. Perhaps limiting the search to one journal has influenced that choice of terminology, though the review has certainly been performed systematically, with clearly set out methodology. Whatever the motivation, the keywords should include review or even systematic review. It might deflect any criticism of not following the PRISMA guidelines, if the authors’ reasons were mentioned in the paper. I should add that I find the presentation by the authors to be satisfactory and the availability of their data, to those interested, offsets the absence of a listing of the included studies and their key findings.</p> <p>There are some minor typos that need correction. In Table 1, the categories for ‘centres outside UK’ total 150 instead of 151. In Table 2, there is a heading “Median (IQR)”. That column only contains the median and the header should be corrected. The second bullet point in ‘Strengths and limitations of this study’ is not strictly accurate. The dates refer to publication dates for the journal and will not correspond with funding dates.</p>
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## VERSION 1 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Robin Prescott

Institution and Country: Emeritus Professor of Health Technology Assessment, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, UK

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

I congratulate Professor Walters and colleagues on an eminently readable and informative paper. There are just a few comments that I would like to make.

1) Any review of clinical trials that is based on those that have had their results published is inevitably in danger of reporting a biased sample of the trials that have been started. Others may fail for various reasons including poor recruitment. In this review of trials that have been published in the NIHR HTA journal from January 2004 to April 2016, the risk of this kind of bias may be appreciably diminished. My own experience of the monitoring of projects funded by the NIHR HTA programme leads me to expect that such failures will have been rare, if they have occurred at all. However, not all readers, particularly those outside the United Kingdom, will have this privileged insight. I wonder if the authors can take their review a little further and can quantify the extent to which the review of published trials reflects the population of trials that have been funded by the NIHR HTA Programme? The grants from this Programme are surely a matter of public record, capable of being checked against the trials identified by this survey. Even more simply, I would expect cooperation from the NIHR in supplying the required information, possibly in an anonymised form if necessary, in view of their common interest in the topic of this paper. If the authors cannot fill this gap, I think it is a topic that can usefully be considered within the Discussion. If the gap can be filled, a review of trials funded by the United Kingdom Health Technology Assessment Programme (as indicated in the title of the paper) will be more valuable than the actual review of just those trials whose results have been published.

The reviewer makes a very good point about possible publication bias. We have amended the title; abstract; strengths and limitations section to make clear that this review is about randomised control trials funded by the United Kingdom's National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme and published in the Health Technology Assessment Journal between 2004 and 2016.

We have added a section to the discussion

“There is a possibility of publication bias as this study is restricted to trials that have had their results published in the NIHR HTA Journal; as not all funded trials are actually published. However the possibility of publication bias is small as a review of projects funded by the NIHR HTA programme, between 2002 and 2011, found that 98% (274/280) published in the programme's journal [34]. The HTA's expectation (in line with their contract) is that all HTA Programme funded studies publish in the NIHR Journals Library, even when they have had to close early because of, for example, poor recruitment. The HTA will ask investigators to include a section /chapter on the challenges faced and lessons learned that will then inform other researchers who might be considering similar research.”

2) I note that this review has excluded cluster randomised trials for sound reasons that are explained within the Inclusion/Exclusion criteria. Figure 1 has a box that explains that 612 reports were excluded as “not a report of an RCT nor a report of a cluster RCT”. This implies that there were no cluster randomised trials within the 778 title and abstracts screened. I find that sufficiently surprising that I think it is worth mentioning directly in the first paragraph of Results. That will avoid any suspicion that the wording of the box could be inexact.

We have revised Figure 1 to make clearer how many reports were reviewed and excluded at the various stages; and can confirm that there were 18 cluster RCTs identified (two of which were feasibility cluster RCTs). A further 15 pilot and feasibility studies were excluded. We have double checked the 15 pilot/feasibility reports and can confirm these were external/standalone pilot/feasibility trials.

3) Another exclusion is the 11 pilot studies. While this is sensible if a pilot study was always the objective, I am aware of situations where a definitive trial has been changed to a pilot study as a result of poor recruitment. No doubt the authors have checked that this is not the case, but explicit mention of this in the paper would remove any doubt.

We have revised Figure 1 to make clearer how many reports were reviewed and excluded at the various stages; and can confirm that there were 18 cluster RCTs identified (two of which were feasibility cluster RCTs). A further 15 pilot and feasibility studies were excluded. We have double checked the 15 pilot/feasibility reports and can confirm these were external/standalone pilot/feasibility trials. We have added a sentence to the text to clarify this.

4) Within the tables, 'other' is sometimes used as a category without further specification. Some of the 'other' categories are quite numerous and I find it slightly disconcerting that there are no footnotes to provide further detail.

We have added footnotes to Table 1 and 5 describing what the "other" categories include.

5) The authors have been careful to describe their study as a review and not a systematic review and, indeed, have not strictly followed the PRISMA guidelines for reporting systematic reviews. Perhaps limiting the search to one journal has influenced that choice of terminology, though the review has certainly been performed systematically, with clearly set out methodology. Whatever the motivation, the keywords should include review or even systematic review. It might deflect any criticism of not following the PRISMA guidelines, if the authors' reasons were mentioned in the paper. I should add that I find the presentation by the authors to be satisfactory and the availability of their data, to those interested, offsets the absence of a listing of the included studies and their key findings.

We have now included the term "review" in the list of key words.

6) There are some minor typos that need correction. In Table 1, the categories for 'centres outside UK' total 150 instead of 151.

We should thank the reviewer for spotting this typo that has now been corrected (N=151).

7) In Table 2, there is a heading "Median (IQR)". That column only contains the median and the header should be corrected.

Changed

8) The second bullet point in 'Strengths and limitations of this study' is not strictly accurate. The dates refer to publication dates for the journal and will not correspond with funding dates.

Changed the bullet point now reads

“This study reports the recruitment and retention rates for 151 single and multi-centre randomised control trials funded by the United Kingdom’s National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme and published in the Health Technology Assessment Journal between 2004 and 2016.”

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Prescott, Robin Emeritus Professor of Health Technology Assessment, Usher Institute of Public Health Sciences and Informatics, University of Edinburgh Medical School, Teviot Place, Edinburgh EH8 9AG Scotland
<b>REVIEW RETURNED</b>	30-Jan-2017

<b>GENERAL COMMENTS</b>	I thank the authors for their responses to my comments. I find the changes fully acceptable and I have no further suggestions to make.
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