PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Individual patient data meta-analysis of self-monitoring of blood pressure (BP-SMART) Protocol paper</th>
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<tbody>
<tr>
<td>AUTHORS</td>
<td>Tucker, Katherine; Sheppard, James; Stevens, Richard; Bosworth, Hayden; Bove, Alfred; Bray, Emma; Godwin, Marshall; Green, Beverly; Hebert, Paul; Hobbs, Richard; Kantola, Ilkka; Kerry, Sally; Magid, David; Mant, Jonathan; Margolis, Karen; McKinstry, Brian; Omboni, Stefano; Ogedegbe, Gbenga; Parati, Gianfranco; Qamar, Nashat; Varis, Juha; Verberk, Willem; Wakefield, Bonnie; McManus, Richard</td>
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VERSION 1 - REVIEW

<table>
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<tr>
<th>REVIEWER</th>
<th>Tom Fahey HRB Centre for Primary Care Research &amp; Department of General Practice, RCSI Medical School Dublin</th>
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<tbody>
<tr>
<td>REVIEW RETURNED</td>
<td>09-Jun-2015</td>
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GENERAL COMMENTS

Thank you for asking me to review this protocol for an individual patient data systematic review and meta analysis.

Overall, it is a clear and well written protocol. I do have some substantive comments for clarification:

Detail concerning intensification of blood pressure medication- more detail concerning the treatment algorithms and BP levels at which treatment recommendations in terms of intensification are initiated in the different RCTs are needed. It is likely that the types of BP lowering drugs and the BP thresholds may be different between RCTs. How will the authors deal with such a problem.

Trial quality- regression analysis is planned in terms of different patient characteristics but the authors do not mention if they are going to examine the impact of RCT quality on blood pressure lowering via ABPM. What about examining important RCT characteristics in terms of randomisation, allocation concealment, differential losses to follow up?

Lastly, I am uncertain whether BMJ Open has a policy about accepting protocols of IPD systematic reviews. If they are published, then I feel that this protocol is an novel and clinically important study.

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Peter Lacy University College London, UK</th>
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<tr>
<td>REVIEW RETURNED</td>
<td>16-Jun-2015</td>
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This manuscript describes the protocol for a systematic review and meta-analysis of randomised controlled studies comparing self-monitoring of blood pressure (BP) against no intervention in patients with hypertension. Whilst a reasonable number of similar systematic reviews and meta-analyses have been already published in people with hypertension, reports have analysed study-averaged data. The present protocol proposes a patient-level data analysis approach. This is important because study-level analyses have demonstrated significant between-study heterogeneity, preventing identification of patient-specific variables potentially contributing to BP-lowering effects associated with self BP monitoring. The planned analysis therefore is important in that it has the potential to contribute significantly to understanding potential mechanisms underlying this effect and in identifying patient groups who might benefit most from self monitoring.

The planned analyses seem appropriate, however there are a few minor points for clarification.

1. The authors highlight use of meta-regression in attempting to explain study heterogeneity but imply that there is an absence of sub-group analyses in previous studies. However, a previous systematic review and meta-analysis reported differences in effect for self monitoring in sub-group analyses (1). In this, differences were shown between various study sub-groups including studies with small sample size, studies using telemonitoring, studies using medication titration in addition to self monitoring and studies in patients on dialysis. Additionally some studies have demonstrated reasonable homogeneity between studies when effects on ambulatory BP has been used as an endpoint though this may relate to a lack of power. Findings of previous preliminary sub-group analyses should be acknowledged.

2. In the study background it is stated that the improvements in BP are thought to be due to an increased number of readings (providing a better estimation of underlying BP). It is not clear how this could be the case in studies where clinic BP is used as a study outcome.

3. Data management selection process – PRISMA point 11b. Articles for inclusion will be independently assessed by two reviewers. Will the selection process make use of formal study quality assessment scores such as Jadad or Chalmers scores?

4. Information sources – PRISMA point 9. The search strategy includes electronic databases (Medline, Embase, Cochrane Library) and searches of reference lists of all retrieved papers. In avoiding selection bias, how will relevant but unpublished data be identified? How will evidence for publication bias be assessed?

5. With regard to ambulatory blood pressure as an outcome measurement which component of ambulatory monitoring (daytime or 24-hour) will be used?

6. Exploratory analyses. In the many exploratory analyses specified do the authors plan to investigate effects on mean arterial blood pressure which has been reported in some studies to exhibit homogeneity between studies?

Reference:

REVIEWER
Fabiana Agena
University of São Paulo School of Medicine Hospital das Clínicas, São Paulo, Brazil

REVIEW RETURNED
22-Jun-2015

GENERAL COMMENTS
This paper is very confused. I didn’t understand the conclusion the authors. This paper needs major review to accept the publication.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. Detail concerning intensification of blood pressure medication- more detail concerning the treatment algorithms and BP levels at which treatment recommendations in terms of intensification are initiated in the different RCTs are needed. It is likely that the types of BP lowering drugs and the BP thresholds may be different between RCTs. How will the authors deal with such a problem.

We agree with the reviewer that these issues are important. We will tabulate the treatment algorithms and targets used for each paper. Most international guidelines use similar BP targets – typically 140/90mmHg for those with essential hypertension. In terms of medication, we anticipate using number of antihypertensive medications rather than type, as in general there are similar effects between classes. We anticipate that there will be differences between the reporting in different studies, but because we have direct access to the original authors as co-investigators, we hope to be able to minimise such issues.

We have added a sentence to the methods to make this clear (analysis p8) “Data will be initially tabulated to include important attributes of each trial and to assess comparability, for example of treatment targets.”

We have clarified that we will extract data on the number of antihypertensive medications prescribed. (p7) “Number of medications prescribed at baseline and follow up”

2. Trial quality- regression analysis is planned in terms of different patient characteristics but the authors do not mention if they are going to examine the impact of RCT quality on blood pressure lowering via ABPM. What about examining important RCT characteristics in terms of randomisation, allocation concealment, differential losses to follow up?

We thank the reviewer for drawing our attention to the issue of trial quality. We confirm that we will assess the potential impact of this on our baseline results which will include all available data. We have added a section to the methods paper on page 6: “Assessment of the quality of included trials is controversial.(19) Self-monitoring studies are generally un-blinded for obvious reasons. We will assess the quality of studies in terms of the presence of randomisation, the methodology of outcome assessment, intention-to-treat analyses and attrition rates.(20) We will initially include all studies, and then perform sensitivity analyses considering the potential effect of excluding studies which may be confounded for these reasons.”
Reviewer 2

1. The authors highlight use of meta-regression in attempting to explain study heterogeneity but imply that there is an absence of sub-group analyses in previous studies. However, a previous systematic review and meta-analysis reported differences in effect for self monitoring in sub-group analyses (1). In this, differences were shown between various study sub-groups including studies with small sample size, studies using telemonitoring, studies using medication titration in addition to self monitoring and studies in patients on dialysis. Additionally some studies have demonstrated reasonable homogeneity between studies when effects on ambulatory BP has been used as an endpoint though this may relate to a lack of power. Findings of previous preliminary sub-group analyses should be acknowledged.

We thank the reviewer and have added a sentence to introduction highlighting this work. (Page 4)

“Subgroup analyses from a previous summary meta-analysis suggests that the observed heterogeneity can be explained in part, due to co-interventions such as telemonitoring and use of self-titration and the setting in which the intervention is delivered. (18)”

2. In the study background it is stated that the improvements in BP are thought to be due to an increased number of readings (providing a better estimation of underlying BP). It is not clear how this could be the case in studies where clinic BP is used as a study outcome.

The reviewer is absolutely correct. We have removed this line from the introduction (Page 4)

3. Data management selection process – PRISMA point 11b. Articles for inclusion will be independently assessed by two reviewers. Will the selection process make use of formal study quality assessment scores such as Jadad or Chalmers scores?

See response 2 to reviewer 1

4. Information sources – PRISMA point 9. The search strategy includes electronic databases (Medline, Embase, Cochrane Library) and searches of reference lists of all retrieved papers. In avoiding selection bias, how will relevant but unpublished data be identified? How will evidence for publication bias be assessed?

We will study the reference lists of included articles and ask contributing authors if they have, or are aware of any unpublished data which might be included in the review. A sentence to this effect has been added (Page 5):

“We will study the reference lists of included articles and ask contributing authors if they have, or are aware of any unpublished data which might be included in the review.”

We will assess whether the summary results of studies not providing data suggest important differences from our IPD results. (Page 9)

To assess publication bias for the primary outcome we will construct an Egger plot, this is now added to Page 9.

“The potential for bias due to non-participation in the IPD will be investigated by comparing aggregate data from eligible trials with and without IPD. Notwithstanding this and the impact of the inclusion criteria (which exclude studies with small populations and /or short follow-up), publication bias for the primary outcome will be explored using Eggar’s methods.(22) For included trials a complete case analysis approach will be used; sensitivity analyses will investigate other methods including, if appropriate, multiple imputation.”

5. With regard to ambulatory blood pressure as an outcome measurement which component of
ambulatory monitoring (daytime or 24-hour) will be used?

We thank the reviewer for identifying the need for clarification here. We plan to use daytime ABPM, defined according to the original study definition (added page 5).

“Outcome - systolic and/or diastolic BP measured in clinic, or by daytime ambulatory measurement.”

6. Exploratory analyses. In the many exploratory analyses specified do the authors plan to investigate effects on mean arterial blood pressure which has been reported in some studies to exhibit homogeneity between studies?

We thank the reviewer for identifying this and have added MAP in the analysis section. (Page 8)

“Exploratory analyses will be conducted (where data are available) including the use and nature of co-interventions (e.g. aimed at medication adherence vs. behavioural change), planned intensity of self-monitoring (i.e. number of home readings), psychosocial factors (e.g. deprivation, quality of life), setting and type of healthcare professional involved (e.g. pharmacist vs. nurse vs. physician), lifestyle factors (e.g. diet, smoking, alcohol consumption, physical activity) and changes in antihypertensive treatment at follow-up and the impact on mean arterial blood pressure (MAP).”

Reviewer 3

1. This paper is very confused. I didn’t understand the conclusion the authors. This paper needs major review to accept the publication.

We hope the changes made in response to the preceding reviewer’s comment clarify this paper. Due to the absence of specific comments from this reviewer we have not made further changes.
Individual patient data meta-analysis of self-monitoring of blood pressure (BP-SMART): a protocol


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Correction


The affiliation for Professor Gianfranco Parati, a co-author on this paper, is incorrect and should be: Department of Cardiovascular, Neural and Metabolic Sciences, San Luca Hospital, Istituto Auxologico Italiano, Milan, Italy & Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy.

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