Author's response to reviews

Title: Auricular acupuncture for prehypertension and stage 1 hypertension: study protocol for a pilot multicentre randomised controlled trial

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Author's response to reviews: see over
Dear Professor Doung Altman, Curt Furberg, Jeremy Grimshaw, and Peter Rothwell

Editors-in-Chief

Trials

We are very pleased to resubmit the manuscript entitled ‘Auricular acupuncture for prehypertension and stage 1 hypertension: study protocol for a pilot multicentre randomised controlled trial’.

We have read editor and reviewer’s remarks carefully and corrected our paper according to their directions. We look forward to hearing from you and the reviewers regarding the suitability of our manuscript for publication.

Thank you.

Yours sincerely

Joo-Hee Kim on behalf of all authors
Referee 1:

Thank you very much for your comments. We have carefully checked and revised the manuscript in an effort to improve it. We hope that you find our revisions to be satisfactory.

Reviewer: François Gueyffier

Reviewer’s report:

The responses from the authors are OK with me, leaving the feeling of a study of limited interest:

- There will not be any possibility to distinguish among several confusion factors separating the two groups, which prevents drawing any conclusion related to the effect of acupuncture by itself; it will not be possible to extrapolate the results in other health system context.

Response: We agree with your comments that sham control is required to assess the non-specific and placebo effects of acupuncture. However, previous experimental and clinical studies have shown that sham acupuncture is not physiologically inert, and the relevance of sham acupuncture as a placebo control has been questioned (Tsukayama et al., 2006; Campbell, 2006). In acupuncture and other complex non-drug interventional trials, unlike in a drug trial, sham control design cannot distinguish the whole placebo effect, and may
lead to false negative results and biases against the treatment being tested (Paterson et al., 2005; Kaptchuk et al., 2006; Birch, 2006).

In addition, we designed this clinical trial to address the effectiveness of an intervention implemented in real-world clinical conditions. Therefore, we used a usual care control group, which is consistent with previous hypertension studies using usual care control groups in pragmatic clinical trials (Edelman et al., 2010; Park et al., 2011). As a pragmatic trial could lead to biases, we have added additional details to the Discussion section (page 12, paragraph 3, line 7- page 13, paragraph 1, line 8).

- References
- The demonstration that blood pressure will be reduced in the acupuncture group will not be a solid reason to recommend acupuncture in hypertensive patients, since blood pressure is a partial surrogate outcome only.

The conduct of such a trial is a huge work. It is a pity that such efforts be conducted with so few chances to draw clinically relevant conclusions. My feelings are shared between the importance that such an amount of work be acknowledged, and the prevention of future investments in similar useless works.

Response: According to your comments, we have added additional details and references to the Discussion section (page 12, paragraph 2, lines 1-7) and the Background section (page 4, paragraph 3, lines 2-6).
Referee 3

Thank you very much for your comments. We have carefully checked and revised the manuscript in an effort to improve it. We hope that you find our revisions to be satisfactory.

Reviewer: Charlie Goldsmith

Reviewer's report:

Some criteria for pilot success should be specified as suggested by Reference 20.

1. Page 5, paragraph 2. Include the stratification here as well as on Page 6.

Response: We have corrected it as per your suggestion (Page 5, p 3, l 6).


Response: We have corrected it as per your suggestion (Page 6, p 3, l 11).

3. Page 6, p 3, l 6 suggests that the sample size of 60 will have to be accommodated in 16 strata: Centre(2), Age(4) and Sex (2). This may mean that some strata may have very few patients in which to accommodate blocking as suggested on l 4.

Response: In the current study, we aim to evaluate the effectiveness of auricular acupuncture in the whole subject pool as the main analysis. This is a pilot study to
investigate clinical evidence, including feasibility, effects, and safety for later use in large-scale auricular acupuncture research; we intend to explore the patterns and tendencies in the data. To improve the distributional balance in both groups, we used stratified randomisation, and we will assess the results in the applicable stratified groups as additional analyses. We have revised the description on P 10, p 5, l 1- P 11, p 1, l 2.

4. P 9, p 1, l 2. Rewrite as [... in at least 1-min ...].

Response: We have corrected it as per your suggestion (P 9, p 2, l 3).

5. P 9, p 2, l 5. Replace [has] by [have].

Response: We have corrected it as per your suggestion (P 9, p 3, l 5).

6. P 10, p 2. Provide Rs for the different types of analyses being proposed.

Response: We have corrected them as per your suggestion (P 10, p 4).

7. P 10, p 3, l 6 to 8. How will this be done? Provide a R.

Response: We have revised the description as per our response to Question 3 (P 10, p 5, l 1- P 11, p 1, l 2).
- References


8. P 13, p 1, l 1. Include the number of patients randomised as of resubmission.

  **Response:** We have corrected the number of patients as per your suggestion (P 13, p 3, l 1).

At the time of manuscript submission, the trial was in the recruitment phase, and 54 patients were recruited. At the time of resubmission, we had already completed patient recruitment and described the status of the trial at the time of the manuscript submission, according to the editorial requests.

9. P 14, l 3. BMI is defined twice; OTC, HDL, and LDL are not defined.

  **Response:** We have corrected them as per your suggestion (P 14, p 3, l 3, 7-9).