Author's response to reviews

Title: Does intermittent pneumatic compression reduce the risk of post stroke deep vein thrombosis? The CLOTS 3 trial: Statistical analysis

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Version: 2 Date: 1 February 2013

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Title: Does intermittent pneumatic compression reduce the risk of post stroke deep vein thrombosis? The CLOTS 3 trial: Statistical analysis plan

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On behalf of the CLOTS trial collaboration

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Dear Sirs

Re: MS: 2228477708603508 - Does intermittent pneumatic compression reduce the risk of post stroke deep vein thrombosis? The CLOTS 3 trial: Statistical analysis plan

Thank you for providing your associate editor’s comments on the above manuscript. We appreciate the intention of making our statistical analysis plan even more robust. However, since we have now locked our trial database and have started our analyses, we feel that it would be inappropriate to change our statistical analysis plan at this stage. If we were to do so we might be criticised for making changes after looking at the data. However, we are very pleased to provide a response to the editor’s comments, especially as it provides an opportunity to clarify certain aspects of our analysis plan. We have addressed each of the three point separately.

I would like authors to consider if there is some way to improve it with the following 3 suggestions.

1) Please consider clarifying that the interim analyses did not include any formal stopping rule that requires adjustment in the final analysis, which would maintain the overall alpha risk at the desired level.

We can confirm that the charter adopted by our independent data monitoring and ethics committee did not include any formal stopping rules.

2) Your final report should be written in accordance with the CONSORT general statement, but including the extension for non-pharmacologic interventions: http://www.consort-statement.org/extensions/interventions/non-pharmacologic-treatment-interventions/

As your trial was designed prior to the publication of this guideline, some aspects may not have been addressed in the protocol, such as: selection criteria for interventionists, or centers; collection of data about interventionists? training and experience; or the way to protect against the risks of performance bias --evaluation bias seems to be already addressed. But, if you have registered a code for the interventionist or the center, you may still consider them as random variables to be included in the statistical model.

As caregivers are not blinded, there is some risk of performance bias (i.e., more additional interventions in the control arm). Please, if feasible, consider including in your statistical analysis plan additional information about extra interventions during follow up.

We thank the editor for pointing out this important document which we will certainly take account of when reporting the results of our trial. Fortunately,
we have collected data on the following aspects: numbers of patients allocated to each treatment group by centre; degree of adherence to the allocated interventions; degree of blinding achieved in assessing the primary outcome; details of some relevant background treatments e.g. graduated compression stockings and antithrombotic medications, which might have differed due to the healthcare staff being unblinded. Although intermittent pneumatic compression is a relatively simple intervention, we did provide standardised training to our centres although successful application of the intervention does not require great skill. Also, many of the items on the extended CONSORT checklist refer to cluster trials which of course ours was not.

3) Recently (http://www.nejm.org/doi/full/10.1056/NEJMsr1203730), NEJM recommended that statistical analysis should be strong enough to convince readers that the results don’t rely on poor assumptions about missing information. I would like you to consider if there are ways to improve your main and sensitivity analyses in order to be more robust against lack of data. Of course, if this number is small enough, you may ignore this advice.”

We are planning sensitivity analyses which treat missing data in different ways. However, given the very small amounts of missing data in our trial we do not plan any interpolation of data items.

Yours sincerely

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