Author's response to reviews

Title: A Cluster Randomized Trial to Assess the Impact of Clinical Pathways for Patients with Stroke: Results of the Clinical Pathways for Effective and Appropriate Care Study

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A Cluster Randomized Trial to Assess the Impact of Clinical Pathways for Patients with Stroke: Results of the Clinical Pathways for Effective and Appropriate Care Study
Massimiliano Panella, Sara Marchisio, Romeo Brambilla, Kris Vanhaecht and Francesco Di Stanislao

Dear Dr. D’Souza,

I hereby would like to thank you for the review of our paper (MS: 1514029948666353) that we submitted to BMC Medicine.

Please find below our cover letter giving a point-by-point response to the concerns and the revised version of our paper.

Best Regards,

Prof. Dr. Massimiliano Panella

(a) Include responses for points 3,4 and 5 to reviewer 1 into the manuscript.

I included the response for points 3, 4, and 5 in the text, that was changed accordingly as follows:

Methods Section, Study sample sub-section (page 6, lines 12-20): “Because of in international literature the mortality of ischemic stroke patients ranged from 8% to 17%, we expected to measure such difference in our sample to be able to evaluate as effective the use of the CP.(3;25;26) We think that this estimation was reasonable because in the pilot study that we performed previously to the main trial, we observed an overall in-hospital mortality of 19.76%, that was consistent with the higher levels of mortality reported in literature.(24) Therefore as 8% to 17% of ischemic stroke patients should die within 30 days of the incident, we expected that the CP would succeed in limiting mortality to 8% and would therefore be clinically relevant.”

Methods Section, Data collection sub-section (page 9, lines 8-17): “The national register is based on local registers that are filled up and used in each Health Authority at the Healthcare District level. These registers are uploaded in real time when a death occurs and there is a monthly matching with the Municipality register for newborn and deaths. The filling up of these registers is compulsory by the doctor that certify the death (both in the hospital or at patients’ home) and there is a national procedure for monitoring diagnosis data quality and reliability. In the case of our study we did not have any particular problems about reliability of diagnosis of death because we followed up 2 cohorts of people affected by ischemic stroke and when a death occurred, we verified the concordance of the cause of death recorded in the register with the pre-existing diagnosis of stroke. The concordance of the 2 diagnosis that was 100%.”

Methods Section, Statistical analysis sub-section (page 9, lines 19-21): “The study design was based on the Framework for design and evaluation of complex interventions by Campbell et al., and on the Consort Statement for cluster Randomized Controlled Trials and the statistical analysis was performed accordingly. (27)”
(b) Please include a clear ethics statement as follows:

Ethics - Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/en/30publications/10policies/b3/index.html), and any experimental research on animals must follow internationally recognized guidelines. A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

The following Ethics subsection has been added to the Methods (page 5 line 15):

Ethics
The project received ethical clearance as a prerequisite of approval for funding from the Italian Ministry of Health. The CPEAC study was approved by the Ethical Committee of Ancona, Marche Region, Italy and the research was carried out in compliance with the Helsinki Declaration. The managers in each unit consented to their clinic taking part in the trial. Patient consent to be randomized to the intervention or control arms was not obtained, because the study design requires randomization to occur at the unit level. All individual patients gave consent to participate in the study and had the opportunity to withdraw from the study at any time. All patient data were managed according to the Italian Data Protection Act.

(c) Adhere to CONSORT guidelines in more detail particularly in the results and discussion section accordingly to the information in the following link: http://www.consort-statement.org/index.aspx?o=1031

The structure of the paper has been revised according to the CONSORT statement: extension to cluster randomised trials.

The RESULTS section has been detailed as it follows:

<table>
<thead>
<tr>
<th>RESULTS</th>
<th>Participant flow</th>
<th>Flow of clusters and individual participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of clusters and participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.</th>
<th>The participation flow has been described in figure 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment</td>
<td>14</td>
<td>Dates defining the periods of recruitment and follow-up.</td>
<td>These information were provided in the METHODS, sub-section Design Overview, page 5 lines 8-9</td>
</tr>
<tr>
<td>Baseline data</td>
<td>15*</td>
<td>Baseline information for each group for the individual and cluster levels as applicable</td>
<td>This section has been added to the RESULTS, please see page 10, line 18</td>
</tr>
<tr>
<td>Numbers</td>
<td>16*</td>
<td>Number of clusters and participants (denominator) in each</td>
<td>The numbers</td>
</tr>
</tbody>
</table>
analyzed group included in each analysis and whether the analysis was by “intention-to-treat”. State the results in absolute numbers when feasible (e.g., 10/20, not 50%).

<table>
<thead>
<tr>
<th>Outcomes and Estimation</th>
<th>17*</th>
<th>For each primary and secondary outcome, a summary of results for each group measures for the individual or cluster level as applicable, and the estimated effect size and its precision (e.g., 95% confidence interval) and a coefficient of intracluster correlation (ICC or k) for each primary outcome.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancillary analyses</td>
<td>18</td>
<td>Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.</td>
</tr>
<tr>
<td>Adverse events</td>
<td>19</td>
<td>All important adverse events or side effects in each intervention group.</td>
</tr>
</tbody>
</table>

The DISCUSSION section has been detailed has it follows:

<table>
<thead>
<tr>
<th>DISCUSSION</th>
<th>20</th>
<th>Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalisability</td>
<td>21*</td>
<td>Generalisability (external validity) to individuals and/or clusters (as relevant) of the trial findings.</td>
</tr>
<tr>
<td>Overall evidence</td>
<td>22</td>
<td>General interpretation of the results in the context of current evidence.</td>
</tr>
</tbody>
</table>

(d) Include an acknowledgement section as follows: We strongly encourage you to include an Acknowledgements section between the Authors & contributions section and Reference list. Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include their source(s) of funding. Please also acknowledge anyone who contributed materials essential for the study. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements. Please list the source(s) of funding for the study, for each author, and for the manuscript preparation in the acknowledgements section. Authors must
describe the role of the funding body, if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

The Acknowledgements section has been added to the document (please see page 15, line 14).