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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Author's response to reviews: see over
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

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<th>Concern by reviewer (R1 &amp; R2)</th>
<th>Response by corresponding author</th>
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<tr>
<td>R1: 1. Abstract – Results – You say that there is a “higher probability of returning to prestroke functioning” but the odds ratio shows a lower probability. I think this requires correction.</td>
<td>We agree with the Reviewer and we changed the sentence accordingly in the abstract (page 2, line 20), as follows: «and significantly lower rates of adverse functional outcomes, expressed as odds of not returning to pre-stroke functioning in their daily life (0.42; 0.18-0.98). »</td>
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<td>R1: 2. Methods – When was the study carried out?</td>
<td>The study carried out from July 2005 to May 2007, please see methods section, design overview, page 5, line 6.</td>
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<td>R1: 3. Methods – Sample size – Can you please clarify the power calculation. Were you estimating a reduction in mortality from 17% to 8%?</td>
<td>Yes, because in international literature the mortality of ischemic stroke patients ranged from 8% to 17% of die within 30 days of the incident, we expected to measure such difference in our sample to be able to evaluate as effective the use of the care pathways (please refer also to our study protocol, reference 15). We think also that our 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 (reference 24. Panella M, Brambilla R, Marchisio S, Di Stanislao F. Reducing stroke in-hospital mortality: organized care is a complex intervention. Stroke. 2008 Nov;39(11):e186. Epub 2008 Sep 18).</td>
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**R1: 4. Methods** – I note they use data from the National Register. Is this information reliable? Do you have some demonstration of its reliability?

We thank the Reviewer for this comment. The Italian National Register of Mortality 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 newborns and deaths. The filling up of these registers is compulsory by the doctor that certifies 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%.

**R1: 5. Statistics** – I think an independent statistical review would be useful.

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.

**R1: 6. Results** – Do you have any information on the characteristics of the services before the study started?

A pilot study to define baseline levels of performance was performed in 2004 (please see Methods section page 5, line 10) and the results were shown in the reference 24. Panella M, Brambilla R, Marchisio S, Di Stanislao F. Reducing stroke in-hospital mortality: organized care is a complex intervention. Stroke. 2008 Nov;39(11):e186. Epub 2008 Sep 18.

**R1: 7. Results** – The seven day mortality result is statistically significant by your predefined criteria.

We thank the Reviewer for this comment. Unfortunately we made a mistake in filling up table 2 and we regret for this. The correct confidence level for univariate in-hospital death rate with 7 days of admission to hospital is 0.15-1.11 with a p value of 0.054. We corrected table 2 accordingly.

**R1: 8. Discussion** – Was there any difference between the services in terms of the access to stroke unit care prior to the trial? I think this requires clarification particularly in view of the results in Table 4.

We agree with the Referee that this could be an important issue. Accordingly to the trial design we did not perform any measurement prior to the trial. Therefore we can not exclude that some difference between the services in terms of the access to stroke unit care could have occurred prior to the trial, and ultimately could have partially biased our results. On the other hand we performed a cluster randomization in order to control such possible confounding factors and no differences at baseline have been observed in hospital characteristics (both arms contained 4 hospitals with a stroke unit). Moreover after
performing the adjusted analysis we did not observe any impact in term of mortality or functional outcomes related to the access to the stroke units. In our study the access to the stroke units, as well as the use of organised care, was planned has an active component promoted by the implementation of the care pathways. Therefore, the observed improvement was expected as a part of the intervention. According to these considerations we re-wrote the Discussion section, page 11, line 23 as follows: «The use of organized care and the access to the stroke units was significantly higher in the CP group. Because stroke unit and organized care are integrated approaches to managing stroke and are strong evidence-based independent predictors of in-hospital mortality, they were used as “active components” promoted by the implementation of the CP.(8;24) Therefore, the observed improvement in organized care and in the use of the stroke units and their positive impact on patients’ outcome were expected as part of the intervention.»

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<th>R1: 9. Discussion – It would be useful to reference the recent cluster randomized study from Australia (Middleton et al, Lancet 2011).</th>
<th>We really thank the Reviewer for this suggestion that could significantly increase the consistence of our findings. Consequently we added the paper by Middleton et al., in our references list, as reference 49 (please see Discussion section, page 13, line 2). We also added the commentary by Wolfe and Rudd as reference 55 in the Discussion section, page 14, line 3. We changed the order of the remaining references accordingly.</th>
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<td>R2: 1. Details of the Care Pathway need to be submitted as an appendix so that it can be assessed and replicated in other settings</td>
<td>We thank the Reviewer for her comment and we provided in the appendix the model care pathway that has been implemented in our study.</td>
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