Author’s response to reviews

Title: Early postoperative cognitive dysfunction and postoperative delirium after anaesthesia with various hypnotics: a double blind, prospective, randomized, controlled clinical trial - The PINOCCHIO trial -

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Author’s response to reviews: see over
Dear Editors,

Thank you for the peer-review feedback and the opportunity to resubmit our manuscript entitled “Early postoperative cognitive dysfunction and postoperative delirium after anaesthesia with various hypnotics: a double blind, prospective, randomized, controlled clinical trial - The PINOCCHIO trial”.

We have replace the term “incidence” by “rate”, the term “range” by “interval” and the term “ranging” by varying” according with your suggestion. We have also added an appendix of all short term used in the text. Finally we have revised the statistical analysis. All corrections made in the text are highlighted in bold.

We have now added postoperative pain evaluation, that can affect the risk of postoperative delirium and have added reference n. 16.

Sincerely,

Federico Bilotta MD, PhD
Department of Anaesthesiology, Critical Care and Pain Medicine, “Sapienza” University of Rome, Policlinico Umberto I, Rome, Italy
1. Page 2, Last line. Replace [Southner] by [Southern].

   We have correct

2. Page 4, Paragraph 2, Line 1. Replace [incidence] by [rate]. Incidence is the rate of conversion from not having an event to having an event over a specified time interval. Since time is not specified here, it is better to use rate. Also Page 5, Paragraph 3, Line 3; Page 9, Paragraph 1, Line 3; Page 11, Paragraph 1, Line 2; Page 18, Paragraph 2, Lines 10, 11; Page 20, Paragraph 2, Line 3.

   We have correct and replace the term [incidence] with [rate]

3. The authors should consider adding an appendix of all the short forms used in the manuscript. Some may be strange to the readers of Trials.

   We have now added the appendix with all of short terms used in the text (page 21)

4. Page 11, Paragraph 2, Line 3. What factors and levels are used for stratification? Or does this refer to blocking?

   Here we refer to patient’s assignment at 1 out of the 3 treatment blocks. No patient stratification will be done at randomization. We have specified in the text (Page 16, Paragraph 2, Line 1): “Patients will be randomly assigned in consecutive order (in allocation blocks of 6 for the first 750 patients and of 3 for the last three patients). No patient stratification will be done”.

5. Page 11, Paragraph 3, Line 2. Does GCS have to be exactly 15 or is it <, or is it >?

   GCS is exactly 15. We have specify this in the text

6. Page 12, Paragraph 3, Line 8. Replace [range] by [interval]. A range is a single number and is the length of an interval. Also Page 13, Paragraph 1, Line 3.

   We have replace [range] by [interval]


   We have replace [time-points] by [times]

We have correct and replace [ranging] by [varying].

9. P 15, p 2. The sample size does not reflect the stratification or the number of centers. Also, the authors should cite the on-line software used to compute the sample size. Presumably the allocation ratio is 1:1:1 and so should be stated here. The analysis of the data does not reflect what possible multiple comparisons will be done, and what if any adjustment will be made for these multiple comparisons. The authors should also comment on the sample size for their proposed subgroups, as they will have less power than the overall study.

We have now substantially changed this paragraph. As now mentioned in the text, sample size calculation has been based on previous evidence reported in literature, we have also specified that software used is PASS2005.

10. P 20, p 1, l 6. Insert a space after the inequality and before the [2].

We have correct

11. The references were not checked for accuracy.

We have correct

12. P 26, R(eference) 4. What is the overlap if any with this study and the one reported in R 4?

The references [3,4] contribute to demonstrate the relationship between delayed postoperative neurocognitive recovery and anesthetics with different pharmacokinetic properties. We have now added a reference that links lower neurocognitive status with delirium.