Author's response to reviews

Title: Update on the Preventive Antibiotics in Stroke Study a randomised controlled phase 3 clinical trial

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Author's response to reviews: see over
Amsterdam, 19th of March 2014

Dear editor,

Herewith we would like to submit our response to the suggested revisions on the update on the protocol of the ‘Preventive Antibiotics in Stroke Study’ (PASS). Our point-by-point response to the concerns:

Major compulsory revisions

1. Please, specify somewhere what kind or ordinal regression (i.e., cumulative, adjacent, …) are you planning to do.

We will perform an ordinal regression analysis according to the proportional odds model, also known as the cumulative logit model. We specified this in the protocol and added a reference (page 4, line 25).

2. Please, specify somewhere if the ordinal nature of the mRS scale will be considered fully ordinal or if some values will be equated in the analysis (i.e, some authors don’t punt a cut-point between 5 and 6: they are pooled in the analysis).

All categories of the mRS scale will be used. All categories of the mRS are shown in figure 1, in addition we added this to the manuscript (page 4, line 28)


The total statistical analysis plan, including treatment of missing values, will be published before the database is closed and the randomisation code is broken. The statistical analysis plan will include treatment of missing values. We have added this in ‘Development of the statistical analysis plan’ (page 6, line 10).

Minor essential Revisions

1. As you specified a PROBE design, there is some risk of performance bias (differential follow up between groups, such as administration of non-scheduled interventions). Please, specify somewhere how will you prevent and control it.

We agree that the PROBE design carries the risk of performance bias. Since the treating physician is aware of the treatment allocation, this could influence decisions on non-scheduled treatment. For the PASS the most important issue to address is the detection and treatment of infection. A physician could be more or less likely to
order investigations or start treatment for a possible infection depending on the treatment allocation. Therefore we collect data on the diagnostic procedures and treatment in all patients in whom infection could be suspected, e.g., patients with fever, a new onset delirium, patients with clinical diagnosis of infection, and patients in whom there was suspicion on infection, but no diagnostics were performed. In this subgroup of patients, diagnosis of infection will be reviewed by a panel of two independent infectious diseases specialists, blinded for treatment allocation. Differences between experts will be resolved by discussion. Recommendations for the diagnostic procedures are a chest X-ray, two blood cultures, urine analysis and urine culture, a sputum culture, leucocyte count and C-reactive protein from a venous blood sample, as specified in the primary protocol publication. We added this limitation of the study to the manuscript (page 5 line 20-26)

2. Please provide details of your dissemination policy, such as those suggested in SPIRIT item 31.

Our dissemination policy, including analysis and publication of trial results, authorship and plans for (public) access to the full protocol, dataset and statistical code, will be specified in the statistical analysis plan, which will be published before randomisation code is broken.

Discretionary revisions

1. As SPIRIT has been published after you designed your initial protocol, please, consider checking your updated protocol fulfil it.

Thank you for suggesting using the ‘Standard Protocol Items: recommendations for intervention trials’, SPIRIT. We used the SPIRIT checklist to assess this update of the PASS protocol and added the following items:

- Item 2b: all items from the WHO trial registration data set. We added a table with these items. We refer to this table on page 3 line 14.
- Item 3: protocol version. We added a table with overview of all protocol amendments since the first version. We refer to this table from page 3 line 17. We also added a sentence describing the medical ethical approval of the protocol and amendments (page 3 line 18).
- Since a few of the SPIRIT items are not again mentioned in this update of the protocol, but are described in the initial protocol, we added a sentence in which we refer to the original protocol (page 3, line 15).

In addition to your comments, we added another change to the update of the protocol. This concerns one of the secondary outcomes, namely the use of antibiotic therapy during 3 months follow-up. We recorded the use of antibiotics during hospital stay, not during the total follow-up time. Therefore we changed this outcome to use of antibiotics during hospital stay (page 3 line 29).

We hope to have sufficiently responded to your concerns and questions.

Sincerely yours,

Willeke Westendorp