Author’s response to reviews

Title: The REstart or STop Antithrombotics Randomised Trial (RESTART) after stroke due to intracerebral haemorrhage: statistical analysis plan for a randomised controlled trial

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Comment to the editor: After the submission of this SAP as a protocol update, the trial statistician checked the planned analyses using dummy treatment groups before database lock and un-blinding. She found that some strata contained null values in the planned sub-group analyses (adjusted for the covariates in the minimisation algorithm), so we revised the categorisation of time since intracerebral haemorrhage for analysis of the MRI sub-study in view of the distribution of outcomes in the whole trial dataset and specified the approach to be followed should any of the multivariate analysis models used with the MRI sub-study data fail to converge. This led to a further modification of the SAP, which is reflected in the revised manuscript and in the final SAP (version 1.7) which is included as an additional file.

We are grateful to the reviewers for their insightful comments, to which we respond point-by-point below:

Reviewer #1:
The authors report the statistical analysis plan of a clinical trial to investigate the benefit and risk of restarting anti platelet medication in survivors of ICH. The manuscript is coherently written, and this is a topic of clinical importance.

Response: Thank you.

I offer the following suggestions:

1) The analysis plan appears to be intention-to-treat. I agree that this is the appropriate approach but would suggest considering the possibility of ancillary per-protocol analysis.

Response: We understand that some readers like to see pre-protocol and as-treated analyses as well as intention-to-treat analyses. However, we pre-specified in the protocol, which was published in Trials, that, “In order to preserve fully the huge benefit of randomisation, we will include all randomised participants in the analysis (irrespective of whether they adhere to the allocated treatment), all retained in the group to which they were allocated (i.e. ‘as-randomised’).” Therefore, we are unable to modify this in the statistical analysis plan.

2) The authors may not have planned this a priori but an analysis with all-cause death as outcome could be interesting and helpful for answering the research question.

Response: We agree that this might be interesting, so we plan to describe the frequencies of all deaths in the two groups. However, because of our concerns about multiple hypothesis testing with a modest number of outcomes from 537 participants and a long list of planned analyses, we will not formally analyse the hazard ratio for all-cause death.

Reviewer #2:

This statistical analysis plan for the RESTART trial provides many details of the rigorous procedures used in this important study. The substance is all excellent (and of course, unlikely to change given the timing). I have a few suggestions that might strengthen this manuscript.

Response: Thank you.

1. Reading this, it is a bit unclear at what time point most participants will be assessed. While this may be covered in the clinical paper - it would be helpful to add this detail here (briefly). Will it generally be during the acute hospitalization, rehab, or in the clinic afterwards?

Response: Unfortunately, we were unable to help the reader by reproducing all of the explanations in the trial protocol. In the protocol published in Trials, which we have cited, we
wrote, “There is no specific time window for identifying participants, so they may be recruited during their hospital admission for the qualifying ICH or at a later stage in an outpatient clinic.”

2. On line 156, I think the word huge can be deleted. "Preserve fully the benefits of randomization" is less bombastic. Most readers of Trials are in favor of randomization.

Response: Thank you, we agree, so we have deleted the

3. I understand that this isn't classically non-inferiority or superiority. That said, you state you are attempting to estimate a "treatment effect." Since the primary outcome is recurrent ICH, and it is unlikely that the antiplatelets will reduce the risk of ICH, I find this a bit confusing. It seems to me the point of this trial is to avoid recurrent thromboembolic events without increasing (substantially) hemorrhage events (mainly ICH). To me, it seems like the mRS analysis is really the most important one (although obviously more complicated) since this captures disabling ischemic and hemorrhagic stroke on the same scale (along with fatal hemorrhage and fatal non-brain thromboembolism like pulmonary embolism). If possible, perhaps expand the discussion so that the reader can better understand the goals. To me, it seems like the treatment effect is reducing disabling events (on the whole), yet the primary analysis is biased as ICH events should be more frequent in patients with anti-thrombotics. Again, I am just not certain if how to interpret your study if the time to recurrent ICH HR is 1.4 in the anti-thrombotic group, yet the mRS is better in that group. I am not expecting a change to you plan - but perhaps some additional context in the discussion would be helpful.

Response: Thank you for this astute observation. We agree that net functional benefit would be the ultimate goal, but we would not expect the sample size in this trial to be able to demonstrate a difference. If any hazardous effects of antiplatelet therapy on recurrent ICH are less than found by the Antithrombotic Trialists Collaboration in 2009 (risk ratio ~1.4) then it might be appropriate to proceed to a further trial to investigate net functional benefit. We added an extra paragraph to the discussion as follows, “The results of this trial will help to estimate, for the first time, the effects of antiplatelet drugs on recurrent ICH. This will provide information about the likely net effects of antiplatelet drugs after ICH, and whether a larger RCT will be required to estimate effects on all serious vascular events or functional outcome.”