Author’s response to reviews

Title: The National Institute for Health Research Hyperacute Stroke Research Centres and the ENCHANTED trial: the impact of enhanced research infrastructure on trial metrics and patient outcomes

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Author’s response to reviews:

Thank you for your positive assessment of our revised manuscript, and for the opportunity to provide a further response to the outstanding comments of your second reviewers on our manuscript. I have annotated the responses to these comments, highlighting where changes have been made in the revised manuscript below.

Reviewer 2:

The authors have provided a rapid response to the review with careful consideration of the comments. Several elements have been addressed and the quality and relevance of the paper have improved. This is an important research study. I still think that it would be useful to explain some of the trial terminology and analyses more clearly for the journal readership.
Response: We apologise for the continued lack of clarity with respect to the terminology and analyses undertaken in respect of the ENCHANTED trial. We have provided more information about the primary and main secondary analyses and their interpretation. We trust that this satisfies the Reviewer, without over-lengthening the manuscript. As outlined in our previous response to Reviewer 1, we were keen to use ENCHANTED as an exemplar study to explore the impact of research infrastructure investment on research performance and patient outcomes, rather than provide excessive detail about the ENCHANTED trial per se. In addition, we have avoided stroke-specific abbreviations, given the readership are likely to be less familiar with these.

One additional question arose when I reread the paper, related to risks of having the research focus of these units, given that the patient profile is different from the traditional stroke unit. Might some "complex" stroke populations be restricted from using these centres because they do not fit the typical profile needed for clinical trials; i.e., exclusion criteria? And therefore, might they miss out on the possible higher quality of care provided at these research/clinical care centres?

Response: The Reviewer raises an important point. However, it is important to state that HSRCs are selected against a number of criteria, including their ability to deliver high quality clinical care, as evidenced across a number of criteria, as well as their track record in research. Whilst a number of these criteria were listed in the revised manuscript, we omitted to add an important selection criterion based on the Sentinel Stroke National Audit Programme (SSNAP) grade of A or B, particularly in key domains relevant to thrombolysis and acute stroke management; namely, door-to-CT scan time, HASU admission within 4 hours, and thrombolysis rates. SSNAP has greater than 95% data ascertainment from hospitals admitting acute stroke patients, and provides a rolling quarterly score of performance across key care domains; A and B reflecting the highest standard of care. This information has been added to the revised manuscript, and we trust reassures the Reviewer that HSRCs deliver high quality clinical care, without restricting the patient population that they serve. In addition, we would draw the Reviewer’s attention to other factors that suggest that HSRCs do not select a ‘less complex’ stroke population: they are often regional neurosciences centres, they admit high patient volumes, and there are other clinical data suggesting they admit severe stroke patients (similar rates of angiographically confirmed large vessel occlusion, and higher rates of clinical diagnosis of large artery occlusion, mechanical thrombectomy, and early ischaemic changes on admission CT scans).

As requested, a tracked version of the revised manuscript has been uploaded, and I can confirm that the revised manuscript has the approval of all authors. On behalf of my co-authors, I trust
that the changes are acceptable to Health Research Policy and Systems, and permit publication of our manuscript.