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 the opportunity to respond to the detailed comments of your reviewers on the aforementioned manuscript. I have annotated the responses to these comments, highlighting where changes have been made in the revised manuscript below.

Reviewer #1:

Many thanks for the opportunity to review the paper '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'. This was a quantitative analysis of UK-based participants recruited to the Alteplase arm of the ENCHANTED clinical trial. The analysis focused on the influence of admission to Hyperacute Stroke Research Centres (HSRCs)
on research performance (e.g. recruitment rates and randomisation to treatment times) and patient outcome (death/mRS status at 90 days).

Substantial public money has been dedicated to the HSRCs, and it is anticipated that greater research activity might be associated with better patient outcomes. There is therefore a need to understand the extent to which these centres have contributed to research performance and patient outcomes.

The paper is written very clearly and communicates the context, approach, findings, and interpretation well; and there is a strong flow of reasoning throughout. My only comment on this aspect of the paper is the fact that so many aspects of the research are reported elsewhere that it can be slightly effortful to access all relevant information. Rather than cross-referring (e.g. under methods), there may be value in adding a couple of further sentences of detail for the less initiated reader.

Response: We are grateful to the Reviewer for their positive comments about the rationale for and presentation of our manuscript. As requested, we have added additional information about the ENCHANTED trial to improve the readability of the manuscript and limit the need to access other journal publications, without significantly extending the length of the manuscript. However, we have limited this study-specific information as ENCHANTED is an exemplar study to enable us to explore the impact of research infrastructure investment on research performance and patient outcomes; the primary focus of the manuscript.

I have a small number of questions about the paper:

1. Design: given there is no comparison of pre Vs post-HSRC status, can we be certain that it is the introduction of HSRC status alone that has led to the higher performance on research performance (e.g. HSRCs might already have been 'high flyers' before they were designated as such in 2010)? As two HSRCs were launched during the ENCHANTED trial, was there any way to look at pre-post performance in these newer centres (a 'natural experiment')? There might be value in reflecting on and communicating the 'pre-HSRC' performance of these centres, or at least acknowledging that this might be a contributing factor.
Response: The Reviewer raises an important point as to whether the benefits seen can be attributed solely to HSRC status. Unfortunately, only one HSRC changed status during the course of the ENCHANTED trial, so this provides limited opportunity for a ‘natural experiment’. However, the Third International Stroke Trial was a similar trial of thrombolysis treatment within a 6-hour time window conducted by the National Institute for Health Research Clinical Research Network, which provides an opportunity to present pre- and post-HSRC data in the revised manuscript.

2. Case mix: the proportion of female patients seems quite low (~41%), and is (non-significantly) lower in HSRCs than non-HSRCs. Have the authors had a chance to reflect on why this might be, and whether this might have implications for interpretation of findings (e.g. possibly to do with age profile of sample, as discussed by Foerch, C., Ghandehari, K., Xu, G., & Kaul, S. (2013)?).

Response: The Reviewer makes a helpful observation that the proportion of female patients is lower than might be expected given the age demographic of stroke, and likely reflects the age profile of the trial population; male predominance in stroke trials is frequently seen. A comment has been added to the revised manuscript. We are also not able to develop a plausible hypothesis as to why the HSRC population has fewer females, though the difference is non-significant and is likely the ‘play of chance’.

3. Diagnosis: there was a significantly higher proportion of patients with large artery occlusion in HSRCs than in non-HSRCs. Patients with such a diagnosis might have been eligible for mechanical thrombectomy, a procedure which might also have influenced outcomes. One would expect HSRCs to also be active in trials of thrombectomy (i.e. more so than non-HSRCs), which could in turn mean patients were benefiting from a separate treatment. Was provision of thrombectomy factored into this analysis (or indeed the trial design) at all?

Response: As the Reviewer has rightly identified, cerebral angiography was more frequently undertaken at HSRCs, as was endovascular therapy. Whilst concomitant therapy according to national guidelines, including the use of mechanical thrombectomy, was permitted in the ENCHANTED trial, overall rates were low at 2% in the UK and 3.8% worldwide. This likely reflects the evolving evidence base for mechanical thrombectomy during the ENCHANTED trial, which was not a funded procedure recommended by the National Institute of health and Care Excellence (NICE) at the time.
4. Organisational factors: might broader 'volume effects' - where services treating a larger number of patients have been associated with - have influenced performance in the HSRCs. There is substantial variation in the volume of patients treated in UK stroke units: were the team able to factor e.g. annual unit activity into their analysis, in order to rule out the possibility that activity levels contributed to the results?

Response: This is an important point, and indeed one of the criteria reviewed in the process of HSRC accreditation was patient volume (target population >1,000 admissions per annum). In addition, there are data, previously published by the Stroke Sentinel National Audit Programme, highlighting the importance of patient volumes outcomes. Accordingly, in the revised manuscript, we have added data about patient volumes to the results section, and addressed the issues related to patients volumes in HSRC designation criteria and outcomes in the revised discussion section.

If necessary, I would be delighted to read a revised version of this important piece of research.

Reviewer #2:

This is very important work but not suitable for a health services and policy journal as it is currently constituted. If the purpose is to focus results toward the importance of sustaining hyperacute stroke units the following is necessary: 1. describe the units in greater depth...2. your trial data need to be explained in terms of the design and analysis for a health services audience. 3. combining of other data that speak to the impact of these centres is needed. I would either focus on the research centre value add or the clinical results and spend more time addressing one or the other because, in the end, its not likely that the NHS would support such centres for their research value.. Who do you want to convince? The value add of these units is not convincing especially since the user profile is quite different from the control population. It feels like a clinical trial paper with a small health services orientation. Is there a health services and policy researcher as a co-author. This may help the team orient the paper more effectively.

Response: We are grateful to the Reviewer for their positive comments on the importance of our work, and in particular the clear guidance to improve the clarity of the purpose of this manuscript; namely to compare (primarily) the research performance and (secondarily) the patient outcomes of Hyperacute Stroke Research Centres (HSRCs), as opposed to Hyperacute
Stroke Units (HASUs). Therefore, in the revised manuscript, we have: (i) provided additional background on HSRCs; (ii) provided more detail on the ENCHANTED trial; and (iii) focused primarily on the added research value (as opposed to clinical value), citing appropriate data to support this. The NHS Constitution highlights the importance of research and research participation, so it is important to highlight the value that HSRCs provide in this regard to NHS commissioners and providers, and this has been emphasised in the revised manuscript. Whilst we appreciate the Reviewer’s comment about a health services and policy researcher as a co-author, it is difficult to address this at this stage in our research. Nonetheless, we trust that the changes to the focus of the manuscript will persuade the Reviewer of the use of trial data to assess the impact of HSRC investment on research metrics.

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.