Reviewer’s report

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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Reviewer: Angus Ramsay

Reviewer's report:

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.

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.

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)?)

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?

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?

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

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