

BMJ - Decision on
Manuscript ID
BMJ.2018.046272

Body:

18th October 2018

Dear Professor Morris

Manuscript ID BMJ.2018.046272 entitled "Impact and sustainability of centralising acute stroke services in English metropolitan areas: retrospective analysis of hospital episode statistics and stroke national audit data"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

If you have any queries please do feel free to get in touch, otherwise we look forward to seeing the revised paper in due course.

Yours sincerely,

Dr Sophie Cook
UK research editor
scook@bmj.com

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****Report from The BMJ's manuscript committee meeting****

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Chair: John Fletcher

Statistician: Jamie Kirkham

Attendees: Sophie Cook,, Elizabeth Older, Daoxin Yin, Tiago Villanueva, Jose Merino

Decision: Put points

Detailed comments from the meeting:

*The statistical analysis section is quite long but is consistent with the approaches used in the 2014 paper.

*We are interested to hear your response to the reviewer's queries about missing data assumptions.

*We think it would be helpful to have more information to help put this into a international context. For example, how does this compare with other countries like Finland, Germany and Australia who have good systems in place? Why is this particular approach important and what does it offer over other models?

*We recognise that stroke unit care has evolved since the stroke unit trials collaboration studies were published (which is mentioned by one reviewer). The concept of a stroke unit is variable and in some countries stroke units include acute care and rehab services while in others they only provide acute care. We think this deserves further comment in the paper.

*Could you provide additional information on how the systems are set up? While this may be available in other papers, would be nice to have a summary, perhaps as a table or side box. In London, for example, are the eight hyper acute stroke units capable of providing thrombolysis alone or can they also provide endovascular therapies? Given that there are 24 stroke units, are there formal agreements between the 8 hyper acute units and these? At what point are patients transferred? How do paramedics identify patients who should go to a hyper acute stroke units? In Manchester, could you discuss comprehensive and primary stroke centers? How do these compare with the hyper acute stroke units in London? Are these designations equivalent to the same designations in the US?

*Could you briefly explain the situation across the rest of the UK? Do other cities have similar systems? Or is the experience from London and Manchester the basis to extend this type of intervention throughout the UK?

*We appreciated the focus on hard outcomes. Information on use of specific interventions is useful as it paints a good picture of hesitation and allows comparisons with other geographical areas. Do you have information on endovascular interventions?

*We noted the first paragraph of the results section describes the important outcomes but it refers to supplementary materials? How think these data should be incorporated into the main paper. We would like to see not only the differences in differences but also the absolute numbers. We are not convinced that the p values in table 1 are useful.

*Figure 2 and figure 3 show mortality and length of stay for London - one editor commented that it appears here that there was a decline before the line (centralisation) and that, if anything, centralisation impaired the improvement - please could you clarify this?

Please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below. Please also respond to these additional comments by the committee above and include in your revision a point by point, response to reviewers document in which you include your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper. Please also include a marked and unmarked copy of the article when you submit your revision.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:

This is an impressive paper that focuses on the changes in emergency stroke care following implementation of a dedicated stroke facility serving Greater Manchester in England during the last few years. The results are impressive and strongly support the development of such programs in Britain and other countries. The paper is complex and the tables are exhaustive. A suggestion would be to limit the data in the tables to those features that are related to care in the first few hours after stroke.

Another observation from the data is that emergency stroke care in other areas of England has been improving as well. This development, which is laudable, may reflect spillover from the efforts in London and Manchester. That may be a subject of another paper.

Additional Questions:

Please enter your name: Harold Adams

Job Title: Professor of Neurology

Institution: University of Iowa

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 2

Recommendation:

Comments:

The authors describe the effects of improving acute stroke care in English metropolitan areas during the past decade. They brought together an impressive amount of data regarding stroke patients in Greater Manchester and London.

Major issue

The paper's main focus is on the effect of centralizing acute stroke care, given the title and all arguments in 'what this study adds'. When reading the paper I am not convinced that the study proves that centralization has led to the borderline

evidence of mortality reduction in Greater Manchester and the significant decline in hospital stay.

This is why:

1. All data in the paper emphasizes that stroke care in Greater Manchester has improved majorly and impressively on all accounts, see Table 3, A6, A7 and figure A2. As the authors themselves already notice in their introduction: 'In Greater Manchester, 39% of stroke patients were admitted to a HASU, whereas in London over 90% of patients were, possibly explaining the difference in mortality outcomes between the two areas'. In the year 2015/16 this number in Greater Manchester has improved towards 86%. I do not find any argument why not this increase (patients that are treated in HASU), has led to improved outcomes, but that this was due to centralization. Personally this appears more plausible to me. It has been known that getting stroke patients on a stroke unit is reducing death, dependency and increasing likelihood of return to home (Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev.). Therefore when considering the presented data, the data shows that treatment in HASU improves outcome of acute stroke patients and this message is not new.

2. Secondly I am troubled with the fact that the primary outcome of the study, that is mortality, is for the largest period of the studied period missing (2008 until april 2013). It is hard to understand what was actually done when referring to expected risks of death while reading the statistical analysis section. It is however clear that the statistical approach is not validated, is fully developed in patients at a specific time point and the missing values are not at random. The generally accepted and promoted option when working with large amounts of missing data is multiple imputation (Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls BMJ 2009; 338).

Minor comments

- It would be insightful to know which patients are currently not admitted to HASU, since not 100% of acute stroke patients are treated in HASU in the latest reported period.
- I do not appreciate the added benefit of the further research proposed by the authors. In my opinion when talking about improving outcome of stroke patients most important steps for a region/nation is to get all stroke patient to a HASU as soon as possible. The fantastic data the authors have at their disposal could be used to identify bottlenecks of the current (regional) approach and systems regarding stroke patients admittance. Identify what patients or regions need improvements and what places could be used as example (London area?). This will get stroke patients better outcomes.
- The second paragraph of the introduction is long and appears better suited for the discussion section.
- Please state in the data methods section the period of mortality data collection, now it is only stated in the abstract.
- Please specify the number of patients per subgroup for stroke type, also in table 1 and 2
- Please specify what diagnoses are possible when regarding to 'stroke, not specified as hemorrhage or infarction'
- Furthermore it is striking that this group has the largest difference-in-differences (table 2), any explanation?
- In table 1 the largest coefficient for difference-in-differences is for ICH -4.1, however not significant, probably due to small number of patients given the largest confidence interval. Any explanation?
- Please enlarge y-axis of figure 2 and start at 0 just as in figure 3.
- It is remarkable that the number of stroke, not specified as hemorrhage or infarction has dramatically fallen from period 1 to 3 for every region, especially in Manchester 26.9% to 7.5%. It appears that this cannot be fully explained by changes in epidemiology so problems in coding seems plausible. Any explanation? How was this handled when analyzing the data and during the analysis?

- The difference-in-differences in table a2 of -1.1 is unnecessary information. Same goes for A4
- I cannot find any information on data completeness.
- I do not see many references to other general papers regarding stroke unit care including the trials such as: Langhorne P, Williams BO, Gilchrist W, Howie K. Do stroke units save lives? Lancet 1993; 342: 395–98. Asplund K, Hulter-Asberg K, Norrving B, for the Riks-stroke collaboration. Riks-Stroke—a Swedish national quality register for stroke care. Cerebrovasc Dis 2003; 15 (suppl 1): 5–7. Langhorne P, Pollock A, in conjunction with the Stroke Unit Trialists' Collaboration. What are the components of effective stroke unit care? Age Ageing 2002; 31: 365–71. Indredavik B. Stroke units—the Norwegian experience. Cerebrovasc Dis 2003; 15 (suppl 1): 19–20. Hommel M, Deblasi A, Garambois K, Jaillard A. The French stroke program. Cerebrovasc Dis 2003; 15 (suppl 1): 11–13. Bereczki D, Csiba L, Fulesdi B, Fekete I. Stroke units in Hungary—the Debrecen experience. Cerebrovasc Dis 2003; 15 (suppl 1): 23–25. 9 Sterzi R, Micieli G, Candelise L, on behalf of the PROSIT collaborators. Cerebrovasc Dis 2003; 15 (suppl 1): 16–18. 10 Czlonkowska A, Milewska D, Ryglewicz D. The Polish experience in early stroke care. Cerebrovasc Dis 2003; 15 (suppl 1): 14–15. 11 Melo TP, Ferro JM. Stroke units and stroke services in Portugal. Cerebrovasc Dis 2003; 15 (suppl 1): 21–22. Busse O. Stroke units and stroke services in Germany. Cerebrovasc Dis 2003; 15 (suppl 1): 8–10. Brainin M, Steiner M, for the participants in the Austrian Stroke Registry for Acute Stroke Units. Acute stroke units in Austria are being set up on a national level following evidence-based recommendations and structural quality criteria. Cerebrovasc Dis 2003; 15 (suppl 1): 29–32. Sulter G, Elting JW, Langedijk M, Maurits NM, De Keyser J. Admitting acute ischemic stroke patients to a stroke care monitoring unit versus a conventional stroke unit: a randomised pilot study. Stroke 2003; 34: 101–04.

Additional Questions:

Please enter your name: Maxim Mulder

Job Title: MD, PhD

Institution: Erasmus University MC

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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Reviewer: 3

Recommendation:

Comments:

Drs. Annemieke Lenselink
CVA patient & research participant

Additional Questions:

Please enter your name: Annemieke.lenselink@gmail.com

Job Title: Patient Reviewer

Institution: Private

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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Reviewer: 4

Recommendation:

Comments:

The authors show that reorganisation of stroke care can have a yield for survival of stroke patients. The biggest effect is shown when all patients suspected of stroke were sent to designated stroke centers. Strength of the study is that this effect was shown in two districts. It was even shown in one district (Manchester) that when the new concept was only introduced partly the effect was much smaller.

To consider the impact of this reorganisation to the full some more data are needed.

What was the definition of suspected stroke? Who defined the patients as suspected stroke? How were health workers instructed? What was the effect on total number of patients admitted to the designated centers? In what part of the patients suspected of stroke was there an effect on waiting time in the ER or excess to CT-scan for other patients?

The analysis of the data is solid and it is strong that effect is shown on most if not all outcome indicators.

Achievements are however modest compared to results in other countries, even if they do not have this centralised approach. Comparison with other countries is missing and this should be reflected in the literature. But reported results are important.

I think this paper in a revised form may well be worth publishing.

Table 1: 'stroe unit' should be 'stroke unit'

Additional Questions:

Please enter your name: M.C. Visser

Job Title: neurologist

Institution: Amsterdam UMC

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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Reviewer: 5

Recommendation:

Comments:

The manuscript analyzes the effects of the centralization of stroke services in large urban areas in the framework of the British healthcare system on 4 outcomes; on the proportion of patients treated in a hyperacute stroke unit, on the application rate of evidence-based clinical interventions, on the length of hospital stay and on 90-day case fatality. Two real-life models were analyzed, one in London and the other one in Greater Manchester. In London a complete centralization (i.e. practically all acute stroke patients get their treatment in hyperacute stroke units) was performed in 2010, and this system has been maintained since then. In Manchester partial

centralization was performed in 2010, only stroke patients with stroke onset of less than 4 hours were admitted to hyperacute stroke units. In a second step in 2015, Manchester changed to the London system, i.e. regardless of the time elapsed from stroke onset, all patients were admitted to hyperacute stroke units. The authors basically found that the improvement in the 4 outcomes of interest was maintained in London between 2010 and 2016, and the outcomes in Manchester improved after the total centralization introduced in 2015, compared to the system using the 4-hour limit between 2010-2015.

The numbers presented are clear and convincing. The results of this study are important, especially for the reason that if they can be generalized, these experiences will have large effect in (re)organizing stroke services in many regions of the world. Mainly for this reason, I recommend to address a few issues in the discussion of the manuscript.

1./ The manuscript is based on healthcare administrative data, therefore presumably considers only hospitalized stroke patients. The possible effect of hospital admission rate in acute stroke (and its change over the years) should be mentioned. E.g. in the Oxfordshire Community Stroke Project over 40% of patients with first-ever stroke did not get to hospital within the first month after their stroke (Bamford J, Sandercock P, Warlow C, Gray M. Why are patients with acute stroke admitted to hospital? *Br Med J* 1986;292:1369-1372.). In a report 14 years later the rate of those not hospitalized was still over 20% (Alexander H, Bugge C, Hagen S, Russell E. Incidence, hospital admission rate, and health outcomes following stroke in Ayrshire and Arran. *Health Bull Edinb.* 2000;58:408-413.). Decreased case fatality in the recently introduced hyperacute stroke units may be due to a higher hospital admission rate in the new centralized system, i.e. those with minor signs (thus having better prognosis) who previously were not admitted to hospital (see Bamford et al, referenced above) may also get hospitalized in the better organized new system, i.e. an important baseline prognostic factor may differ between the pre-centralization and post-centralization periods.

2./ Death is not the only important outcome after stroke. Case fatality may decrease on the price of increasing the proportion of disabled/dependent survivors. The authors mention in the discussion that they have some data on disability at six months after stroke. Even if these data are not absolutely accurate, the value of the manuscript certainly would increase if in addition to case fatality, the combined outcome of „death and dependency“ could be presented in the comparisons.

3./ There are general trends in decreasing stroke incidence and stroke severity not directly related to the service system. The risk-adjusted overall 90-day case fatality marginally decreased in Manchester after introducing total centralization (95 CI: minus 2.7 to plus 0.01 for differences-in-differences). As stroke mortality is clearly related to socioeconomic factors, it should be addressed if such a change in overall fatality may be related to an increase in living standard over this period.

4./ The largest difference-in-differences (although with the widest confidence intervals) in case fatality was found not for ischemic strokes but for intracerebral hemorrhages (Table 1). The proportion of those with intracerebral hemorrhage in this study is 11-13% (Table A6). As the motivation for reorganizing stroke services around the world is mostly for the improvement of outcome for ischemic strokes (new methods for recanalization), it will be important for the readers to see a subgroup analysis of the results separately for ischemic strokes.

5./ The length of stay (LOS) on acute or hyperacute stroke units largely depends on the availability of rehabilitation units and the local agreements between the acute and rehabilitation services on the time of transmission of stroke patients from the acute stroke unit to the rehabilitation unit. The decrease of LOS on stroke units may be explained by earlier transmission of patients to rehab units. The authors should comment on this in the discussion.

Sincerely,

Daniel Bereczki, MD, DSc, FESO

Additional Questions:

Please enter your name: Daniel Bereczki

Job Title: department chairman, vice dean, professor of neurology

Institution: Semmelweis University, Department of Neurology

Reimbursement for attending a symposium?: No

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