Report from The BMJ's manuscript committee meeting

1. 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 have added more information about the international context in the Introduction (first paragraph). In the "Strengths and weaknesses in relation to other studies" section of the Discussion we highlight there are alternative models to the 'hub-and-spoke' model.

2. 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.
We have added a comment in the Introduction (first paragraph) to say there is variation within and between countries in both access to stroke unit care and organisational models within stroke units; we also cite supporting literature.

3. 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?
We have provided further details of both models as requested; see the "The centralisations" section of the Methods. Note that the CSCs and PSCs in Greater Manchester are not equivalent to CSCs and PSCs in North America.

4. 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 now explain in the "Meaning of the study" section of the Discussion that currently there has been limited implementation of the 'hub-and-spoke' model for stroke across the UK, and that based on the experiences in London and Greater Manchester other areas of the UK are considering system-wide reconfiguration of acute stroke services; we also provide some examples.

5. 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 did not request data from SSNAP on thrombectomy so unfortunately we cannot provide any data on this. The reason we did not request these data is that SSNAP only started requiring that data on thrombectomy be collected (i.e., added it to the core dataset) from October 2015, i.e., after the centralisations in London and Greater Manchester took place. This means we would be unable to evaluate the impact of the system-wide changes we are investigating on use of these interventions.

In terms of the current state of play with regards thrombectomy, according to the 2016 SSNAP Organisational audit (https://www.strokeaudit.org/Documents/National/AcuteOrg/2016/2016-AcuteOrgEAV.aspx), Standard 6 outlines the proportion of hospitals offering access to thrombectomy (whether onsite or by transferring patients elsewhere); 66% of hospitals in England meet this standard, though this may not necessarily be an onsite service.

During the time period we studied (up to March 2016) thrombectomy *was* provided in a limited way. For example, St George's in London was the first site in the UK to offer a 24/7 thrombectomy service, but this only began in October 2016. (https://wwww.stgeorges.nhs.uk/service/neuro/stroke/mechanical-thrombectomy/). NHS England announced in April 2017 that it will begin commissioning mechanical thrombectomy services. (https://www.england.nhs.uk/2017/04/stroke-patients-in-england-set-to-receive-revolutionary-new-treatment/)

In the "Unanswered questions and future research" section of the Discussion we now say that further work to investigate the impact of introducing thrombectomy services into the acute stroke pathway would be beneficial.

6. We noted the first paragraph of the results section describes the important outcomes but it refers to supplementary materials? We 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.
We have moved the details of the unadjusted difference-in-differences analysis (referred to in the first paragraph of the Results) from the Supplementary material into the main text of the paper, with a new Table 1.

We have added the absolute numbers 'either side' of the difference-in-differences to Tables 1 and 2 (now Tables 2 and 4). As explained in footnotes in both tables it is not possible to recover the absolute numbers directly from the statistical method we have used. To see this, the final statistical model we use to estimate the difference-in-differences is:

$$y_{it} = \alpha + \beta_i + \gamma_t + \delta D^1_{it}.D^2_{it} + \varepsilon_{it}$$

where y_{it} is the outcome of interest (mortality, length of stay) for trust i in month j, α is a constant term, β are trust fixed effects, γ are month fixed effects, and ε is an error term. D^1 is an indicator variable =1 if the observation is in Greater Manchester (=0 otherwise) and D^2 is an indicator variable =1 if the observation is in the period after the centralisation in Greater Manchester in 2015 (=0 otherwise). The interaction of D^1 and D^2 identifies hospitals in Greater Manchester after the centralisation, and δ is the difference-in-differences estimate. The main effects of D^1 and D^2 are omitted from this model as they are perfectly collinear with the trust fixed effects (β) and time fixed effects (γ), respectively. However, it is these main effects that are required to estimate the absolute numbers requested. We prefer the main analysis to use the statistical model described above (i.e., using trust and month fixed effects) rather than including the main effects of D^1 and D^2 instead, as this allows us to more thoroughly control for the impact of time and hospital in our analysis, which we think is important. Instead, to provide the absolute numbers as requested we use an alternative approach, estimating the following:

$$y_{it} = \alpha + \beta_i + \gamma_t + \theta D^2_{it} + \varepsilon_{it}$$

separately for Greater Manchester (D^1 =1) and the rest of England (D^1 =0), where θ is the change in the outcome over time in each area following the centralisation. We then use this to compute predictive margins for the outcome for each area (i.e., the predicted value of the

outcome in each area before and after the centralisation) and report this in the tables as the absolute numbers that were requested. However, we would like to point out that:

$$\theta|_{D^1=1} - \theta|_{D^1=0} \neq \delta$$

We explain this in intuitive terms in the footnote to each table.

The P values from Tables 1 and 2 (now Tables 2 and 4) have been removed.

7. 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?
The *x*-axis on the Figures 2 and 3 is quarter (i.e., 3 month period), and the vertical lines indicate the quarter July-September 2010. The centralisation in London was fully operational by July 2010, though some SUs and HASUs were implemented before then (for example, UCLH and St Georges were both operating as HASUs from February 2010).
https://islondon.files.wordpress.com/2012/06/mountford-et-al-2010-reconfiguring-stroke-care-in-north-central-london_hbs-special-edition.pdf
https://www.stgeorges.nhs.uk/wp-content/uploads/2013/11/Stroke-pathway-doc-jan-2013.doc
Therefore, the decline seen in both figures before the vertical line is a function of the fact that some HASUs were operational before July 2010; we have now explained this in the footnotes of the two figures.

Reviewer 1

8. 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.
We thank the reviewer for this comment, but prefer to keep the tables as is to cover care during the whole of the first 72 hours, which relates to the period of time patients typically spend in the HASU.

9. 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.
We have added further details to the Discussion about the "spillover" from the experiences in London and Greater Manchester to other areas of the UK – see also the response to point 4 above.

Reviewer 2

10. 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:

a. 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.

The reviewer is correct in his interpretation of the findings – that (1) the improvement in clinical outcomes in Greater Manchester was largely as a result of more patients being treated in the HASU, and (2) this happened because of the centralisation. However, the reviewer seems to see this as a limitation of the study – we do not think it is because this was precisely the goal of centralisation, which is what we are evaluating. We now explain very clearly in the Introduction (first paragraph) that acute stroke services are centralised into 'hub-and-spoke' systems as one means of improving access to organised inpatient stroke unit (e.g., HASU) care.

b. 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 untill 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).

The reviewer is not right when he says that "the primary outcome of the study, that is mortality, is for the largest period of the studied period missing (2008 until April 2013)." We believe he may have mis-read the "Data" section in the Methods, where we describe the two different datasets used in the analysis. In the first paragraph of the "Data" section we describe the dataset used to investigate mortality and length of hospital stay (i.e., Hospital Episode Statistics); we explain that our dataset covers the period between 1 January 2008 and 31 March 2016; at the end of the first paragraph we provide the numbers of observations (patients) in each time period. Then, in the second paragraph of the "Data" section in the Methods we discuss the dataset used to investigate evidence-based clinical interventions (i.e., national audit data from SSNAP). It is this dataset that covers the period 1st April 2013 to 31st March 2016. The reviewer seems to have interpreted this to mean that our mortality analysis covers the period 1st April 2013 to 31st March 2016, which is incorrect. We apologise if this was unclear, and have added subheadings to avoid any further confusion.

In terms of the reviewer's comment that our statistical approach is not validated, we now point out (see the first paragraph of the "statistical analysis" section of the Methods) that a similar method was used in our previous study published in the BMJ, and prior to that in an evaluation of the advancing quality initiative in the northwest of England (Sutton M, Nikolova S, Boaden R, et al. Reduced mortality with hospital pay for performance in England. N Engl J Med 2012;367:1821-8).

11. 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.

We have added data on the characteristics of patients not treated at a HASU in Greater Manchester during the period after the 2015 centralisation to Table A1 in the Supplementary

material (alongside the other summary statistics from the Hospital Episode Statistics database).

12. 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.
We have added an additional suggestion of further research (see the "Unanswered questions and future research" section of the Discussion, to understand how to improve access to HASU care for all stroke patients.

13. The second paragraph of the introduction is long and appears better suited for the discussion section.
We understand the point made by the reviewer, but have kept this paragraph where it is as we believe it provides important background information for the reader about the present study, describing our previous study and other relevant research.

14. Please state in the data methods section the period of mortality data collection, now it is only stated in the abstract.
This is already given in the first sentence of the "Data" section in the Methods. "To investigate mortality and length of hospital stay we obtained patient-level data from the Hospital Episode Statistics (HES) database[18] for all patients in England with a primary diagnosis of stroke […] between 1 January 2008 and 31 March 2016..."

15. Please specify the number of patients per subgroup for stroke type, also in table 1 and 2
This information is provided in Table A1 in the Supplementary material; we have now made this clear in the main text of the paper. Given that the numbers vary by outcome measure, stroke type, time period and region, adding them to Tables 1 and 2 (now Tables 2 and 4) as suggested by the reviewer would make these tables very difficult to read, so we prefer to not report these figures as the reviewer suggests.

16. Please specify what diagnoses are possible when regarding to 'stroke, not specified as hemorrhage or infarction'
Usually the ICD-10 code I64 (stroke, not specified as hemorrhage or infarction) refers to cases where the cause of the stroke (haemorrhage or infarction) is unknown or has not been documented in the medical record for other reasons. We have added this point to the "Data" section in the Methods.

17. Furthermore it is striking that this group has the largest difference-in-differences (table 2), any explanation?
In Table 2 (now Table 4), showing difference-in-differences in length of acute hospital stay, the decline is largest in the I64 sub-group. We suspect the better length of stay outcomes for this group following the centralisation in Greater Manchester are a function of faster and more comprehensive access to diagnostic testing on arrival at the hospital (especially in patients admitted to a HASU), and partly as a consequence of this, a decline in the number of patients falling into this group. We have now added these points to the paper (fifth paragraph of the "Outcomes" section of the Results).

18. 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?
We agree with the review that the lack of significant impact in the ICH group may be due to the relatively small numbers of patients in the group, and now make this point in the paper(fifth paragraph of the "Outcomes" section of the Results).

19. Please enlarge y-axis of figure 2 and start at 0 just as in figure 3.
We redrew Figure 2 with the y-axis starting at 0 and it makes the line after the point where centralisation occurred appear much flatter (i.e., more likely to show the effects in London were sustained). As a consequence, we prefer to keep Figure 2 as is, as this is more likely to be able to highlight variations in outcomes after centralisation. We have highlighted in the footnote to Figure 2 that the *y*-axis does not start at zero.

20. 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?
As noted above in response to point 17 we believe the decline in the numbers of patients in this group in Greater Manchester over time is probably due to faster and more comprehensive access to diagnostic testing on arrival at the hospital (especially in patients admitted to a HASU). This means that more stroke patients will have a definitive diagnosis of the cause of their stroke. We now make this point in the paper (fifth paragraph of the "Outcomes" section of the Results). The decline is not a problem for our analysis because we either analyse the different stroke types separately, or when we analyse all stroke types together we control for the stroke diagnosis, removing the effect of variations in stroke sub-types over time.

21. The difference-in-differences in table a2 of -1.1 is unnecessary information. Same goes for A4
As requested by the BMJ's manuscript committee we have moved Table A2 into the main paper – it is now Table 1. We prefer to retain the full, simple difference-in-differences calculation on the unadjusted data as it helps to clarify and illustrate the main analytical approach we have used.

22. I cannot find any information on data completeness.
We now explain in the paper that the mortality data were complete (see first paragraph of the "Data" section of the Methods), but that for the analysis of length of hospital stay we dropped 3% observations with missing or excessive length of hospital stay (acute hospitalisation in excess of 120 days).

23. 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.

Given the focus of the paper is to evaluate system-wide centralisation of stroke services into a hub-and-spoke model we do not think it is worthwhile to provide details of the substantial body of literature showing the benefits of stroke unit care. Instead, in the Introduction we now make it clearer that there is a wealth of evidence showing that organised inpatient stroke unit care is associated with better quality of care and reduced death and dependency, referring to three key papers. We go on to say that acute stroke services are centralised into 'hub-and-spoke' systems as one means of improving access to organised inpatient stroke unit care.

Reviewer 3

No comments

Reviewer 4

24. 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?

In the "The centralisation" section of the Methods we have added further information about how suspected stroke cases were identified (using the FAST test) and who identified them (ambulance staff), and where ambulance staff transported patients to depending on, e.g., the postcode, traffic conditions, and capacity at different HASUs.

Unfortunately, we do not have data on the total number of patients admitted to each of the HASUs in London and Greater Manchester before and after the centralisations, nor do we have data to examine whether waiting times in the ED or access to CT scans for non-stroke patients were affected by the centralisations. We do know from SSNAP data (see Table A2 in the Supplementary material) that in the year before the 2015 centralisation in Greater Manchester the number of stroke patients treated in one of the three HASUs was 2389; in the year following the centralisation the number was 3,849, a 61% increase.

25. Comparison with other countries is missing and this should be reflected in the literature. But reported results are important.

In the Introduction (first paragraph) we now explain the situation in some other countries in more detail (see also the response to comment 1, above).

26. Table 1: 'stroe unit' should be 'stroke unit'
Text amended.

Reviewer 5

27. The manuscript is based on healthcare adminsitrative 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.
We now discuss this issue in the "Strengths and weaknesses" section of the Discussion. We point out that the main limitation of our study is the lack of data on stroke severity; this is important because if, for example, the reviewer's hypothesis is correct then we might observe the average level of severity among those who are hospitalised falls as people who previously were not admitted to hospital may now get hospitalised. In the Discussion section we refer to data presented in the Supplementary material, which indicates there were no differences in worst level of consciousness in first 24 hours after stroke over time in stroke patients admitted to hospital in Greater Manchester and London.

28. 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.
We appreciate the importance of the issue raised by the reviewer, but note that data on disability and dependence collected in SSNAP at six month follow-up assessments are not collected reliably enough at present to analyse. For example, six month assessments were undertaken for 30% of applicable patients in April 2015 – March 2016. https://www.strokeaudit.org/Documents/National/Clinical/AugNov2016/AugNov2016-CCGLHBPublicReport.aspx. We now discuss this in further detail in the "Strengths and weaknesses" section of the Discussion.

29. 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.

We agree with the reviewer, and this is precisely the reason why we have used a difference-in-differences study design, to account for variations over time that affect all stroke patients.

30. 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 intracerbral 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 separataley for ischemic strokes.
We agree with the reviewer about the importance of stratifying by types of stroke. We present our analyses of clinical outcomes for all stroke subtypes combined, and also separately for each sub-type (see Results).

31. 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.
We have added this point to the “Strengths and weaknesses” section of the Discussion.